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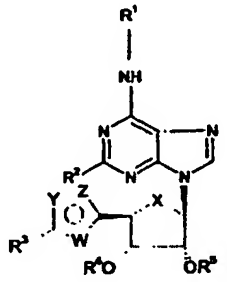
(54) Title: ADENOSINE DERIVATIVES



(I)

(57) Abstract

A compound of formula (I) which is an agonist at the adenosine A1 receptor, wherein Y, Z and W represent heteroatoms, and salts and solvates thereof, in particular, physiologically acceptable solvates and salts thereof for use in therapy.

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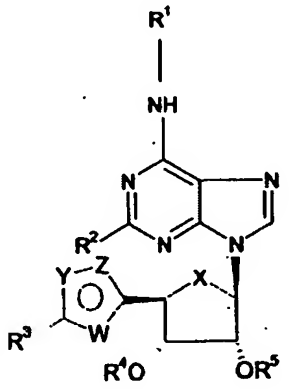
ADENOSINE DERIVATIVES

The present invention relates to novel adenosine derivatives, to processes for their preparation, to pharmaceutical compositions containing them and to their use in medicine.

Publications in this area include WO 98/16539 (Novo Nordisk A/S) which describes adenosine derivatives for the treatment of myocardial and cerebral ischaemia and epilepsy; WO 98/04126 (Rhone-Poulenc Rorer Pharmaceuticals Inc.) which relates to adenosine derivatives possessing antihypertensive, cardioprotective, anti-ischaemic and antilipolytic properties; and WO 98/01459 (Novo Nordisk A/S) which describes N,9-disubstituted adenine derivatives which are substituted in the 4' position by unsubstituted oxazolyl or isoxazolyl and the use of such compounds for the treatment of disorders involving cytokines in humans.

Thus the invention provides a compound of formula (I) which is an agonist at the adenosine A1 receptor



(I)

wherein X represents O or CH_2;

R^2 represents C_{1-3}alkyl, C_{1-3}alkoxy, halogen or hydrogen;

R^3 represents H, phenyl (optionally substituted by halogen), a 5 or 6 membered heteroaryl group, C_{1-6} alkoxy, C_{1-6} alkyl$O(CH_2)_n$ where n is 0-6, C_{3-7} cycloalkyl, C_{1-6} hydroxyalkyl, halogen or a C_{1-6} straight or branched alkyl, C_{1-6} alkenyl or C_{1-6} alkynyl group optionally substituted by one or more halogens.

Y and Z represent O, N, CH, N(C_{1-6} alkyl)
W represents CH, O, N, S, N(C_{1-6} alkyl)
and wherein at least one of W and Z represents a heteroatom (and when Y, Z and/or W is N, the presence or absence of an additional H would be apparent to a person skilled in the art)
with the proviso that when W represents CH, Z represents N and Y represents O, R^3 cannot be H.

R^4 and R^5 independently represent H or a C_{1-6} straight chain or branched alkyl group.

R^1 represents hydrogen or a group selected from

(1) -$(alk)_n$ – (C_{3-7}) cycloalkyl, including bridged cycloalkyl, said cycloalkyl group optionally substituted by one or more substituents selected from OH, halogen, -(C_{1-3}) alkoxy, wherein (alk) represents C_{1-3} alkylene and n represents 0 or 1.

(2) an aliphatic heterocyclic group of 4 to 6 membered rings containing at least one heteroatom selected from O, N or S, optionally substituted by one or more substituents selected from the group consisting of –(C_{1-3})alkyl, -CO_2-(C_{1-4})alkyl, -$CO(C_{1-3}$alkyl), -$S(=O)_n$-(C_{1-3}alkyl), -$CONR^aR^b$ (wherein R^a and R^b independently represent H or C_{1-3}alkyl) or =O; where there is a sulfur atom in the heterocyclic ring, said sulfur is optionally substituted by $(=O)_n$, where n is 1 or 2.

(3) Straight or branched C_{1-12} alkyl, optionally including one or more O, $S(=O)_n$ (where n is 0, 1 or 2) and N groups substituted within the alkyl chain, said alkyl optionally substituted by one or more of the following groups, phenyl, halogen, hydroxy, C_{3-7} cycloalkyl or NR^aR^b wherein R^a and R^b independently represent hydrogen, C_{3-7} cycloalkyl or a C_{1-6} straight chain or branched alkyl optionally substituted by C_{3-7} cycloalkyl;

(4) a fused bicyclic aromatic ring

wherein B represents a 5 or 6 membered heterocyclic aromatic group containing 1 or more O, N or S atoms, wherein the bicyclic ring is attached to the nitrogen atom of formula (I) via a ring atom of ring A and ring B is optionally substituted by $-CO_2-(C_{1-3}alkyl)$.

(5) a phenyl group optionally substituted by one or more substituents selected from:

-halogen, $-SO_3H$, $-(alk)_nOH$, $-(alk)_n$ –cyano, $-(O)_n$ $-(C_{1-6})$alkyl (optionally substituted by one or more halogens), $-(alk)_n$ –nitro, $-(O)_m$ $-(alk)_n-$ CO_2R^c, $-(alk_n)-$ $CONR^cR^d$ $-(alk)_n$ $-COR^c$, $-(alk)_n$ $-SOR^e$, $-(alk)_n$ $-SO_2R^e$, $-(alk)_n-$ $SO_2NR^cR^d$, $-(alk)_nOR^c$, $-(alk)_n$ $-(CO)_m-$ $NHSO_2R^e$, $-(alk)_n-$ $NHCOR^c$, $-(alk)_n-$ NR^cR^d wherein m and n are 0 or 1 and alk represents a C_{1-6}alkylene group or C_{2-6} alkenyl group.

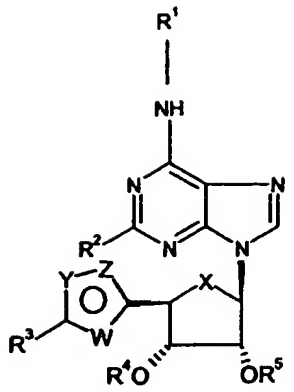
(6) A phenyl group substituted by a 5 or 6 membered heterocyclic aromatic group, said heterocyclic aromatic group optionally being substituted by C_{1-3}alkyl or NR^cR^d.

R^c and R^d may each independently represent hydrogen, or C_{1-3} alkyl or when part of a group NR^cR^d, R^c and R^d together with the nitrogen atom may form a 5 or 6 membered heterocyclic ring optionally containing other heteroatoms, which heterocyclic ring may optionally be substituted further by one or more C_{1-3} alkyl groups.

R^e represents C_{1-3}alkyl

and salts and solvates thereof, in particular, physiologically acceptable solvates and salts thereof for use in therapy.

Preferably the compound is of formula (Ia)



(Ia)

wherein X represents O or CH_2;

R^2 represents C_{1-3}alkyl, C_{1-3}alkoxy, halogen or hydrogen;

R^3 represents H, phenyl (optionally substituted by halogen), a 5 or 6 membered heteroaryl group, C_{1-6} alkoxy, C_{1-6} straight or branched alkyl optionally substituted by one or more halogens, C_{3-7} cycloalkyl, C_{1-6} hydroxyalkyl or halogen.

Y and Z represent O, N, CH
W represents CH, O, N, S
and wherein at least one of W and Z represents a heteroatom (and when Y, Z and/or W is N, the presence or absence of an additional H would be apparent to a person skilled in the art)
with the proviso that when W represents CH, Z represents N and Y represents O, R^3 cannot be H.

R^4 and R^5 independently represent H or a C_{1-6} straight chain or branched alkyl group.

R^1 represents a group selected from

(1) -$(alk)_n$ – (C_{3-7}) cycloalkyl, including bridged cycloalkyl, said cycloalkyl group optionally substituted by one or more substituents selected from OH, halogen, -(C_{1-3}) alkoxy, wherein (alk) represents C_{1-3} alkylene and n represents 0 or 1.

(2) an aliphatic heterocyclic group of 4 to 6 membered rings containing at least one heteroatom selected from O, N or S, optionally substituted by one or more substituents selected from the group consisting of –(C_{1-3})alkyl, -CO_2-(C_{1-4})alkyl, -$CO(C_{1-3}$alkyl), -$S(=O)_n$-$(C_{1-3}$alkyl), -$CONR^aR^b$ (wherein R^a and R^b independently represent H or C_{1-3}alkyl) or =O; where there is a sulfur atom in the heterocyclic ring, said sulfur is optionally substituted by $(=O)_n$, where n is 1 or 2.

(3) Straight or branched C_{1-12} alkyl, optionally including one or more O, $S(=O)_n$ (where n is 0, 1 or 2) and N groups substituted within the alkyl chain, said alkyl optionally substituted by one or more of the following groups, phenyl, halogen, hydroxy, C_{3-7} cycloalkyl or NR^aR^b wherein R^a and R^b independently represent hydrogen, C_{3-7} cycloalkyl or a C_{1-6} straight chain or branched alkyl optionally substituted by C_{3-7} cycloalkyl;

(4) a fused bicyclic aromatic ring

wherein B represents a 5 or 6 membered heterocyclic aromatic group containing 1 or more O, N or S atoms, wherein the bicyclic ring is attached to the nitrogen atom of formula (I) via a ring atom of ring A and ring B is optionally substituted by –CO_2 –$(C_{1-3}$alkyl).

(5) a phenyl group optionally substituted by one or more substituents selected from:

-halogen, -SO_3H, -$(alk)_nOH$, -$(alk)_n$ –cyano, -$(O)_n$ –(C_{1-6})alkyl (optionally substituted by one or more halogens), - $(alk)_n$ –nitro, -$(O)_m$ –$(alk)_n$- CO_2R^c, -(alk_n)- $CONR^cR^d$ –$(alk)_n$ –COR^c, -$(alk)_n$ –SOR^e, -$(alk)_n$ –SO_2R^e, -$(alk)_n$-$SO_2NR^cR^d$, -$(alk)_nOR^c$, -$(alk)_n$ –$(CO)_m$- $NHSO_2R^e$, -$(alk)_n$- $NHCOR^c$, -$(alk)_n$-NR^cR^d wherein m and n are 0 or 1 and alk represents a C_{1-6}alkylene group or C_{2-6} alkenyl group.

(6) A phenyl group substituted by a 5 or 6 membered heterocyclic aromatic group, said heterocyclic aromatic group optionally being substituted by C_{1-3}alkyl or NR^cR^d.

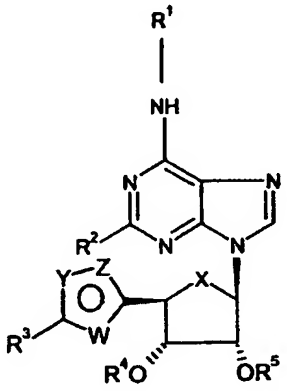
R^c and R^d may each independently represent hydrogen, or C_{1-3} alkyl or when part of a group NR^cR^d, R^c and R^d together with the nitrogen atom may form a 5 or 6 membered heterocyclic ring optionally containing other heteroatoms, which heterocyclic ring may optionally be substituted further by one or more C_{1-3} alkyl groups.

R^e represents C_{1-3}alkyl

and salts and solvates thereof, in particular, physiologically acceptable solvates and salts thereof.

The invention further provides pharmaceutical compositions of formula (I) or (Ia) together with a pharmaceutically acceptable diluent or carrier.

It will be appreciated that certain compounds embraced by formula (I) are novel per se. A particular group of compounds may be defined by formula (Ib). Therefore, the invention further provides compounds of formula (Ib) which are agonists at the adenosine A1 receptor



(Ib)

wherein X represents O or CH_2;

R^2 represents C_{1-3}alkyl, C_{1-3}alkoxy, halogen or hydrogen;

R^3 represents H, phenyl (optionally substituted by halogen), a 5 or 6 membered heteroaryl group, C_{1-6} alkoxy, C_{1-6} alkylO$(CH_2)_n$ where n is 0-6, C_{3-7} cycloalkyl, C_{1-6} hydroxyalkyl, halogen or a C_{1-6} straight or branched alkyl, C_{1-6} alkenyl or C_{1-6} alkynyl group optionally substituted by one or more halogens.

Y and Z represent O, N, CH, N(C_{1-6} alkyl)
W represents CH, O, N, S, N(C_{1-6} alkyl)
and wherein at least one of W and Z represents a heteroatom (and when Y, Z and/or W is N, the presence or absence of an additional H would be apparent to a person skilled in the art)
with the proviso that when W represents CH, Z represents N and Y represents O, R^3 cannot be H.

R^4 and R^5 independently represent H or a C_{1-6} straight chain or branched alkyl group.

R^1 represents hydrogen or a group selected from

(1) -$(alk)_n$ – (C_{3-7}) cycloalkyl, including bridged cycloalkyl, said cycloalkyl group optionally substituted by one or more substituents selected from OH, halogen, -(C_{1-3}) alkoxy, wherein (alk) represents C_{1-3} alkylene and n represents 0 or 1.

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(3) Straight or branched C_{1-12} alkyl, optionally including one or more O, S(=O)$_n$ (where n is 0, 1 or 2) and N groups substituted within the alkyl chain, said alkyl optionally substituted by one or more of the following groups, phenyl, halogen, hydroxy, C_{3-7} cycloalkyl or NR^aR^b wherein R^a and R^b independently represent

hydrogen, C_{3-7} cycloalkyl or a C_{1-6} straight chain or branched alkyl optionally substituted by C_{3-7} cycloalkyl;

(4) a fused bicyclic aromatic ring

wherein B represents a 5 or 6 membered heterocyclic aromatic group containing 1 or more O, N or S atoms, wherein the bicyclic ring is attached to the nitrogen atom of formula (I) via a ring atom of ring A and ring B is optionally substituted by $-CO_2-(C_{1-3}alkyl)$.

(5) a phenyl group optionally substituted by one or more substituents selected from:

-halogen, $-SO_3H$, $-(alk)_nOH$, $-(alk)_n$ –cyano, $-(O)_n$ $-(C_{1-6})$alkyl (optionally substituted by one or more halogens), $-(alk)_n$ –nitro, $-(O)_m$ $-(alk)_n-$ CO_2R^c, $-(alk_n)-$ $CONR^cR^d$ $-(alk)_n$ $-COR^c$, $-(alk)_n$ $-SOR^e$, $-(alk)_n$ $-SO_2R^e$, $-(alk)_n-$ $SO_2NR^cR^d$, $-(alk)_nOR^c$, $-(alk)_n$ $-(CO)_m-$ $NHSO_2R^e$, $-(alk)_n-$ $NHCOR^c$, $-(alk)_n-$ NR^cR^d wherein m and n are 0 or 1 and alk represents a C_{1-6}alkylene group or C_{2-6} alkenyl group.

(6) A phenyl group substituted by a 5 or 6 membered heterocyclic aromatic group, said heterocyclic aromatic group optionally being substituted by C_{1-3}alkyl or NR^cR^d.

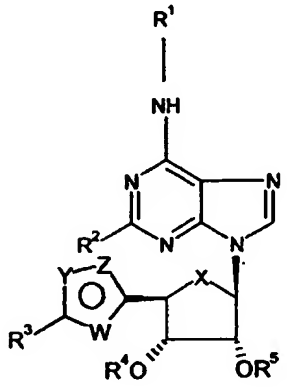
R^c and R^d may each independently represent hydrogen, or C_{1-3} alkyl or when part of a group NR^cR^d, R^c and R^d together with the nitrogen atom may form a 5 or 6 membered heterocyclic ring optionally containing other heteroatoms, which heterocyclic ring may optionally be substituted further by one or more C_{1-3} alkyl groups.

R^e represents C_{1-3}alkyl

with the proviso that when R^4 and R^5 both represent H, R^2 represents halogen, R^3 cannot represent methyl, ethyl, n-propyl, isopropyl, cyclopropyl, $CH(OH)CH_3$, C_{1-3}alkoxy

and salts and solvates thereof, in particular, physiologically acceptable solvates and salts thereof.

Preferably, the compound is of formula (Ic):



(Ic)

wherein X represents O or CH_2;

R^2 represents C_{1-3}alkyl, C_{1-3}alkoxy, halogen or hydrogen;

R^3 represents H, phenyl (optionally substituted by halogen), a 5 or 6 membered heteroaryl group, C_{1-6} alkoxy, C_{1-6} straight or branched alkyl optionally substituted by one or more halogens, C_{3-7} cycloalkyl, C_{1-6} hydroxyalkyl or halogen.

Y and Z represent O, N, CH
W represents CH, O, N, S
and wherein at least one of W and Z represents a heteroatom (and when Y, Z and/or W is N, the presence or absence of an additional H would be apparent to a person skilled in the art)
with the proviso that when W represents CH, Z represents N and Y represents O, R^3 cannot be H.

R^4 and R^5 independently represent H or a C_{1-6} straight chain or branched alkyl group.

R^1 represents a group selected from

(1) -$(alk)_n$ – (C_{3-7}) cycloalkyl, including bridged cycloalkyl, said cycloalkyl group optionally substituted by one or more substituents selected from OH, halogen, -(C_{1-3}) alkoxy, wherein (alk) represents C_{1-3} alkylene and n represents 0 or 1.

(2) an aliphatic heterocyclic group of 4 to 6 membered rings containing at least one heteroatom selected from O, N or S, optionally substituted by one or more substituents selected from the group consisting of –(C_{1-3})alkyl, -CO_2-(C_{1-4})alkyl, -$CO(C_{1-3}$alkyl), -$S(=O)_n$-(C_{1-3}alkyl), -$CONR^aR^b$ (wherein R^a and R^b independently represent H or C_{1-3}alkyl) or =O; where there is a sulfur atom in the heterocyclic ring, said sulfur is optionally substituted by $(=O)_n$, where n is 1 or 2.

(3) Straight or branched C_{1-12} alkyl, optionally including one or more O, $S(=O)_n$ (where n is 0, 1 or 2) and N groups substituted within the alkyl chain, said alkyl optionally substituted by one or more of the following groups, phenyl, halogen, hydroxy, C_{3-7} cycloalkyl or NR^aR^b wherein R^a and R^b independently represent hydrogen, C_{3-7} cycloalkyl or a C_{1-6} straight chain or branched alkyl optionally substituted by C_{3-7} cycloalkyl;

(4) a fused bicyclic aromatic ring

wherein B represents a 5 or 6 membered heterocyclic aromatic group containing 1 or more O, N or S atoms, wherein the bicyclic ring is attached to the nitrogen atom of formula (I) via a ring atom of ring A and ring B is optionally substituted by –CO_2 –(C_{1-3}alkyl).

(5) a phenyl group optionally substituted by one or more substituents selected from:

-halogen, $-SO_3H$, $-(alk)_nOH$, $-(alk)_n$ –cyano, $-(O)_n$ $-(C_{1-6})$alkyl (optionally substituted by one or more halogens), $-(alk)_n$ –nitro, $-(O)_m$ $-(alk)_n-CO_2R^c$, $-(alk_n)-CONR^cR^d$ $-(alk)_n$ $-COR^c$, $-(alk)_n$ $-SOR^e$, $-(alk)_n$ $-SO_2R^e$, $-(alk)_n-SO_2NR^cR^d$, $-(alk)_nOR^c$, $-(alk)_n$ $-(CO)_m-NHSO_2R^e$, $-(alk)_n-NHCOR^c$, $-(alk)_n-NR^cR^d$ wherein m and n are 0 or 1 and alk represents a C_{1-6}alkylene group or C_{2-6} alkenyl group.

(6) A phenyl group substituted by a 5 or 6 membered heterocyclic aromatic group, said heterocyclic aromatic group optionally being substituted by C_{1-3}alkyl or NR^cR^d.

R^c and R^d may each independently represent hydrogen, or C_{1-3} alkyl or when part of a group NR^cR^d, R^c and R^d together with the nitrogen atom may form a 5 or 6 membered heterocyclic ring optionally containing other heteroatoms, which heterocyclic ring may optionally be substituted further by one or more C_{1-3} alkyl groups.

R^e represents C_{1-3}alkyl

with the proviso that when R^4 and R^5 both represent H, R^2 represents halogen, R^3 cannot represent methyl, ethyl, n-propyl, isopropyl, cyclopropyl, $CH(OH)CH_3$, C_{1-3}alkoxy

and salts and solvates thereof, in particular, physiologically acceptable solvates and salts thereof.

Conveniently the adenosine A1 agonists of the general formula (I) above exhibit greater activity at the adenosine A1 receptor than the other adenosine receptor subtypes, particularly A3. More particularly the compounds exhibit little or no agonist activity at the the A3 receptor.

It will be appreciated that wherein R^1 and/or R^2 in compounds of formula (I) contain one or more asymmetric carbon atoms the invention includes all diastereoisomers of compounds of formula (I) and mixtures thereof. Otherwise

the stereochemical configuration of compounds of the invention is as depicted in formula (I) above.

As used herein, the term "alkyl" means a straight or branched chain alkyl group. Examples of suitable alkyl groups within R^1 and R^2 include methyl, ethyl, n-propyl, l-propyl, n-butyl, s-butyl, t-butyl and 2,2-dimethylpropyl.

As used herein, the term "alkylene" means a straight or branched chain alkylene group containing 1-6 carbon atoms, e.g. methylene.

As used herein, the term "C_{2-6}alkenyl" means a straight or branched chain alkenyl group containing 2 to 6 carbon atoms. Allyl represents an example of a suitable C_{2-6}alkenyl group.

The term "halogen" means fluorine, chlorine, bromine or iodine.

By aliphatic heterocyclic group defined for R^1 is meant a cyclic group of 4-6 carbon atoms wherein one or more of the carbon atoms is/are replaced by heteroatoms independently selected from nitrogen, oxygen or sulfur. This group may optionally be substituted as defined hereinabove.

The term heterocyclic aromatic group defined for R^1 refers to an aromatic mono or bicyclic ring system comprising from 5 to 10 carbon atoms wherein one or more of the carbon atoms is/are replaced by heteroatoms independently selected from nitrogen, oxygen and sulfur, which ring system may optionally be substituted as defined hereinabove.

Pharmaceutically acceptable salts of the compounds of formula (I) include those derived from pharmaceutically acceptable inorganic and organic acids. Examples of suitable acids include hydrochloric, hydrobromic, sulphuric, nitric, perchloric, fumaric, maleic, phosphoric, glycollic, lactic, salicylic, succinic, toluene-p-sulphonic, tartaric, acetic, citric, methanesulphonic, formic, benzoic, malonic, naphthalene-2-sulphonic and benzenesulphonic acids. A particularly suitable pharmaceutically acceptable salt of the compounds of formula (I) is the hydrochloride salt. Other acids such as oxalic, while not, in themselves

pharmaceutically acceptable, may be useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable acid addition salts. The solvates may be, for example, hydrates.

Examples of W, Y and Z containing heterocyclic groups include isoxazoles, oxadiazoles, pyrazoles, oxazoles, triazoles and thiadiazoles.

Preferred W, Y and Z containing heterocyclic groups are isoxazoles, and 1,2,4- and 1,3,4- oxadiazoles.

R^2 preferably represents hydrogen, methyl, methoxy or halogen, more preferably hydrogen or chlorine.

Conveniently, R^1 may represent $(alk)_n$- C_{3-6} cycloalkyl wherein n is 0 or 1 and the said cycloalkyl is either substituted by at least one substituent selected from halogen, particularly fluorine, and OH or is unsubstituted. Preferably n is zero. More preferably, the cycloalkyl group is unsubstituted or monosubstituted with OH and more preferably the cycloalkyl ring has 5 carbon members. Most preferably, the cycloalkyl group is hydroxycyclopentyl.

Alternatively R^1 may represent a substituted or unsubstituted aliphatic heterocyclic group, the substitutent being selected from the group consisting of $-CO_2-(C_{1-4})$alkyl.

Conveniently, the aliphatic heterocyclic group is unsubstituted or when the substituent is $-CO_2(C_{1-4})$alkyl, the heteroatom is N and the substituent is directly attached to said ring nitrogen atom.

Preferably the heterocyclic ring is 6 membered and more preferably contains only one O, N or S heteroatom. Most preferably when the heterocyclic ring is unsubstituted the heteroatom is O. Most preferably when the heterocyclic ring is substituted the heteroatom is N.

Alternatively, R^1 may represent a straight or branched alkyl of 1-6 carbon atoms optionally with at least one $S(=O)_n$ and where $S(=O)_n$ is present, optionally substituted with N at a position adjacent to the $S(=O)_n$ group; where there is an $S(=O)_n$ in the chain, substitution with N at a position adjacent to the $S(=O)_n$

group is preferred; where there is an $S(=O)_n$ in the chain, preferably n is 1 or 2, more preferably n is 2. The alkyl group conveniently may be unsubstituted or substituted by at least one OH group.

Alternatively R^1 may represent a phenyl group which is substituted by one or two substituents selected from OH, alkyl, particularly C_{1-4} alkyl and halogen. Preferably the phenyl is disubstituted in the 2,4 positions. Preferably both substituents are halogen more particularly, fluorine and chlorine. For example, a particularly preferred combination is 2-fluoro and 4-chloro.

Preferably R^4 and R^5 represent hydrogen.

It is to be understood that the present invention covers all combinations of particular and preferred groups mentioned above.

Particular novel compounds include compounds of Examples 1-207 herein below.

Preferred compounds include:
(2S,3S,4R,5R)-2-(5-tert-Butyl-[1,3,4]oxadiazol-2-yl)-5-[6-(tetrahydro-pyran-4-ylamino)-purin-9-yl]-tetrahydro-furan-3,4-diol;
4-{9-[5S-(5-tert-Butyl-[1,3,4]oxadiazol-2-yl)-3R,4S-dihydroxy-tetrahydro-furan-2R-yl]-9H-purin-6-ylamino}-piperidine-1-carboxylic acid ethyl ester;
(2S,3S,4R,5R)-2-(5-Isopropyl-[1,3,4]oxadiazol-2-yl)-5-[6-(tetrahydro-pyran-4-ylamino)-purin-9-yl]-tetrahydro-furan-3,4-diol;
4-{9-[5S-(5-Cyclopropyl-[1,3,4]oxadiazol-2-yl)-3R,4S-dihydroxy-tetrahydro-furan-2R-yl]-9H-purin-6-ylamino}-piperidine-1-carboxylic acid ethyl ester;
(2S,3S,4R,5R)-2-(5-tert-Butyl-[1,3,4]oxadiazol-2-yl)-5-[6-(4-chloro-2-fluoro-phenylamino)-purin-9-yl]-tetrahydro-furan-3,4-diol;
(2S,3S,4R,5R)-2-(5-Ethyl-oxazol-2-yl)-5-[6-(tetrahydro-pyran-4-ylamino)-purin-9-yl]-tetrahydro-furan-3,4-diol;
(2S,3S,4R,5R)-2-(3-Cyclopropyl-[1,2,4]oxadiazol-5-yl)-5-[6-(2S-hydroxy-cyclopent-(S)-ylamino)-purin-9-yl]-tetrahydro-furan-3,4-diol;
(2S,3S,4R,5R)-2-(3-tert-Butyl-[1,2,4]oxadiazol-5-yl)-5-[6-(2S-hydroxy-cyclopent-(S)-ylamino)-purin-9-yl]-tetrahydro-furan-3,4-diol;

(2S,3S,4R,5R)-2-(3-Cyclopropyl-[1,2,4]oxadiazol-5-yl)-5-[6-(tetrahydro-pyran-4-ylamino)-purin-9-yl]-tetrahydro-furan-3,4-diol;
(2S,3S,4R,5R)-2-(3-tert-Butyl-isoxazol-5-yl)-5-[6-(tetrahydro-pyran-4-ylamino)-purin-9-yl]-tetrahydro-furan-3,4-diol;
ethyl 4-({9-[(2R,3R,4S,5S)-3,4-dihydroxy-5-(3-methyl-1,2,4-oxadiazol-5-yl)tetrahydrofuran-2-yl]-9H-purin-6-yl}amino)piperidine-1-carboxylate;
(2S,3S,4R,5R)-2-[3-(tert-butyl)-1,2,4-oxadiazol-5-yl]-5-{6-[(cyclopropylmethyl)amino]-9H-purin-9-yl}tetrahydrofuran-3,4-diol;
(2S,3S,4R,5R)-2-[3-(tert-butyl)-1,2,4-oxadiazol-5-yl]-5-[6-(isobutylamino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol;
(2R,3R,4S,5S)-2-[6-(cyclopropylamino)-9H-purin-9-yl]-5-(3-isopropyl-1,2,4-oxadiazol-5-yl)tetrahydrofuran-3,4-diol;
2-({9-[(2R,3R,4S,5S)-3,4-dihydroxy-5-(3-isopropyl-1,2,4-oxadiazol-5-yl)tetrahydrofuran-2-yl]-9H-purin-6-yl}amino)-N-methylethanesulfonamide;
(2R,3R,4S,5S)-2-[6-(3,4-difluoroanilino)-9H-purin-9-yl]-5-(3-isopropyl-1,2,4-oxadiazol-5-yl)tetrahydrofuran-3,4-diol;
(2R,3R,4S,5S)-2-[6-(4-chloro-2-fluoroanilino)-9H-purin-9-yl]-5-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)tetrahydrofuran-3,4-diol;
(2R,3S,4R,5R)-2-[5-(tert-butyl)-4H-1,2,4-triazol-3-yl]-5-[6-(4-chloro-2-fluoroanilino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol;
(2R,3R,4S,5R)-2-[6-(2-chloro-4-fluoroanilino)-9H-purin-9-yl]-5-(5-isopropyl-4H-1,2,4-triazol-3-yl)tetrahydrofuran-3,4-diol;
(2S,3S,4R,5R)-2-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)-5-[6-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol;
(2S,3S,4R,5R)-2-[5-(tert-butyl)-1,3,4-oxadiazol-2-yl]-5-[6-(2-chloro-4-fluoroanilino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol;
(2S,3S,4R,5R)-2-[3-(tert-butyl)isoxazol-5-yl]-5-{6-[(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)amino]-9H-purin-9-yl}tetrahydrofuran-3,4-diol;
2-[(9-{(2R,3R,4S,5S)-5-[5-(tert-butyl)-1,3,4-oxadiazol-2-yl]-3,4-dihydroxytetrahydrofuran-2-yl}-9H-purin-6-yl)amino]-N-ethylethanesulfonamide;
2-[(9-{(2R,3R,4S,5S)-5-[5-(tert-butyl)-1,3,4-oxadiazol-2-yl]-3,4-dihydroxytetrahydrofuran-2-yl}-9H-purin-6-yl)amino]-N-(3-methylphenyl)ethanesulfonamide;
2-({9-[(2R,3R,4S,5S)-3,4-dihydroxy-5-(5-methyl-1,3-oxazol-2-yl)tetrahydrofuran-2-yl]-9H-purin-6-yl}amino)-N-methylethanesulfonamide;

(2R,3R,4S,5S)-2-[6-(cyclopentylamino)-9H-purin-9-yl]-5-[3-(methoxymethyl)-1,2,4-oxadiazol-5-yl]tetrahydrofuran-3,4-diol;
(2S,3S,4R,5R)-2-(5-ethyl-1,3,4-oxadiazol-2-yl)-5-[6-(isopropylamino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol;
(2R,3R,4S,5S)-2-(6-{[(1S,2S)-2-hydroxycyclopentyl]amino}-9H-purin-9-yl)-5-(5-methyl-1,3,4-oxadiazol-2-yl)tetrahydrofuran-3,4-diol;
(2R,3R,4S,5S)-2-{2-chloro-6-[(1-ethylpropyl)amino]-9H-purin-9-yl}-5-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)tetrahydrofuran-3,4-diol formate (1:2);
(2R,3R,4S,5S)-2-[2-Chloro-6-(1-ethyl-propylamino)-purin-9-yl]-5-(3-cyclopropyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol diformate;
(2S,3S,4R,5R)-2-(3-ethylisoxazol-5-yl)-5-[6-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol;
(2S,3S,4R,5R)-2-(3-ethylisoxazol-5-yl)-5-(6-{[(1S,2S)-2-hydroxycyclopentyl]amino}-9H-purin-9-yl)tetrahydrofuran-3,4-diol;
ethyl 4-({9-[(2R,3R,4S,5S)-5-(3-ethylisoxazol-5-yl)-3,4-dihydroxytetrahydrofuran-2-yl]-9H-purin-6-yl}amino)piperidine-1-carboxylate;
(2R,3S,4R,5R)-2-[5-(tert-butyl)-4H-1,2,4-triazol-3-yl]-5-[6-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol;
(2R,3S,4R,5R)-2-(5-isopropyl-4H-1,2,4-triazol-3-yl)-5-[6-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol;
(2R,3R,4S,5S)-2-[2-chloro-6-(2-chloro-4-fluoroanilino)-9H-purin-9-yl]-5-(5-methyl-1,3-oxazol-2-yl)tetrahydrofuran-3,4-diol;
(2R,3R,4S,5S)-2-[6-(4-chloro-2-fluoroanilino)-9H-purin-9-yl]-5-(3-methylisoxazol-5-yl)tetrahydrofuran-3,4-diol;
(2R,3R,4S,5S)-2-[6-(4-chloro-2-fluoroanilino)-9H-purin-9-yl]-5-(3-propylisoxazol-5-yl)tetrahydrofuran-3,4-diol;
(2R,3R,4S,5S)-2-[2-chloro-6-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl]-5-(3-ethylisoxazol-5-yl)tetrahydrofuran-3,4-diol;
ethyl 4-({2-chloro-9-[(2R,3R,4S,5S)-5-(3-ethylisoxazol-5-yl)-3,4-dihydroxytetrahydrofuran-2-yl]-9H-purin-6-yl}amino)piperidine-1-carboxylate;
(2R,3R,4S,5S)-2-(2-chloro-6-{[(1S,2S)-2-hydroxycyclopentyl]amino}-9H-purin-9-yl)-5-(3-ethylisoxazol-5-yl)tetrahydrofuran-3,4-diol;
(2R,3R,4S,5S)-2-(2-chloro-6-{[2-(ethylsulfonyl)ethyl]amino}-9H-purin-9-yl)-5-(3-ethylisoxazol-5-yl)tetrahydrofuran-3,4-diol;

(2R,3R,4S,5S)-2-[2-chloro-6-(4-chloro-2-fluoroanilino)-9H-purin-9-yl]-5-(3-ethylisoxazol-5-yl)tetrahydrofuran-3,4-diol;
(2R,3R,4S,5S)-2-[2-chloro-6-(2-chloro-4-fluoroanilino)-9H-purin-9-yl]-5-(3-ethylisoxazol-5-yl)tetrahydrofuran-3,4-diol;
(2R,3R,4S,5S)-2-[2-chloro-6-(2-fluoroanilino)-9H-purin-9-yl]-5-(3-ethylisoxazol-5-yl)tetrahydrofuran-3,4-diol;
(2R,3R,4S,5S)-2-[2-chloro-6-(2-chloroanilino)-9H-purin-9-yl]-5-(3-ethylisoxazol-5-yl)tetrahydrofuran-3,4-diol;
(2R,3R,4S,5S)-2-(6-{[(1S,2S)-2-hydroxycyclopentyl]amino}-9H-purin-9-yl)-5-[3-(hydroxymethyl)isoxazol-5-yl]tetrahydrofuran-3,4-diol;
ethyl 4-[(9-{(2R,3R,4S,5S)-3,4-dihydroxy-5-[3-(hydroxymethyl)isoxazol-5-yl]tetrahydrofuran-2-yl}-9H-purin-6-yl)amino]piperidine-1-carboxylate;
(2S,3S,4R,5R)-2-[3-(hydroxymethyl)isoxazol-5-yl]-5-[6-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol;
(2R,3R,4S,5S)-2-[6-(4-chloro-2-fluoroanilino)-9H-purin-9-yl]-5-(3-ethylisoxazol-5-yl)tetrahydrofuran-3,4-diol;
(2R,3R,4S,5S)-2-[6-(2-chloro-4-fluoroanilino)-9H-purin-9-yl]-5-(3-ethylisoxazol-5-yl)tetrahydrofuran-3,4-diol;
(2S,3S,4R,5R)-2-(3-ethylisoxazol-5-yl)-5-[6-(2-fluoroanilino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol;
(2R,3R,4S,5S)-2-[6-(2-chloroanilino)-9H-purin-9-yl]-5-(3-ethylisoxazol-5-yl)tetrahydrofuran-3,4-diol;
(2S,3S,4R,5R)-2-[5-(tert-butyl)-1,3,4-oxadiazol-2-yl]-5-[6-(piperidin-4-ylamino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol;
(2R,3R,4S,5R)-2-{2-chloro-6-[(1-ethylpropyl)amino]-9H-purin-9-yl}-5-(5-ethylisoxazol-3-yl)tetrahydrofuran-3,4-diol formate;
(2S,3S,4R,5R)-2-(3-bromoisoxazol-5-yl)-5-[6-(4-chloro-2-fluoroanilino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol
(2S,3S,4R,5R)-2-[3-(tert-butyl)isoxazol-5-yl]-5-(6-{[1-(methylsulfonyl)piperidin-4-yl]amino}-9H-purin-9-yl)tetrahydrofuran-3,4-diol
(2S,3S,4R,5R)-2-[3-(tert-butyl)isoxazol-5-yl]-5-(6-{[1-(propylsulfonyl)piperidin-4-yl]amino}-9H-purin-9-yl)tetrahydrofuran-3,4-diol
(2S,3S,4R,5R)-2-[3-(tert-butyl)isoxazol-5-yl]-5-(6-{[1-(isopropylsulfonyl)piperidin-4-yl]amino}-9H-purin-9-yl)tetrahydrofuran-3,4-diol

(2S,3S,4R,5R)-2-[3-(tert-butyl)isoxazol-5-yl]-5-(6-{[1-(ethylsulfonyl)piperidin-4-yl]amino}-9H-purin-9-yl)tetrahydrofuran-3,4-diol
(2S,3S,4R,5R)-2-[3-(tert-butyl)isoxazol-5-yl]-5-[2-chloro-6-(4-chloro-2-fluoroanilino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol
(2S,3S,4R,5R)-2-[3-(tert-butyl)isoxazol-5-yl]-5-[2-chloro-6-(2-chloro-4-fluoroanilino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol
2-[(9-{(2R,3R,4S,5S)-5-[3-(tert-butyl)isoxazol-5-yl]-3,4-dihydroxytetrahydrofuran-2-yl}-2-chloro-9H-purin-6-yl)amino]-N-ethylethanesulfonamide
2-[(9-{(2R,3R,4S,5S)-5-[3-(tert-butyl)isoxazol-5-yl]-3,4-dihydroxytetrahydrofuran-2-yl}-2-chloro-9H-purin-6-yl)amino]-N-isopropylethanesulfonamide
(2S,3S,4R,5R)-2-[3-(tert-butyl)isoxazol-5-yl]-5-[2-chloro-6-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol
(2R,3R,4S,5S)-2-[6-(4-chloro-2-fluoroanilino)-9H-purin-9-yl]-5-(3-pyridin-3-ylisoxazol-5-yl)tetrahydrofuran-3,4-diol
(2R,3R,4S,5S)-2-[6-(4-chloro-2-fluoroanilino)-9H-purin-9-yl]-5-[3-(4-hydroxybutyl)isoxazol-5-yl]tetrahydrofuran-3,4-diol
2-[(9-{(2R,3R,4S,5S)-5-[3-(tert-butyl)isoxazol-5-yl]-3,4-dihydroxytetrahydrofuran-2-yl}-9H-purin-6-yl)amino]-N-ethylethanesulfonamide
(2R,3R,4S,5S)-2-[6-(cyclopentylamino)-9H-purin-9-yl]-5-[5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl]tetrahydrofuran-3,4-diol
(2R,3R,4S,5S)-2-(6-{[(1S,2S)-2-hydroxycyclopentyl]amino}-9H-purin-9-yl)-5-[5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl]tetrahydrofuran-3,4-diol
ethyl 4-[(9-{(2R,3R,4S,5S)-3,4-dihydroxy-5-[5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl]tetrahydrofuran-2-yl}-9H-purin-6-yl)amino]piperidine-1-carboxylate
(2R,3R,4S,5S)-2-[6-(4-chloro-2-fluoroanilino)-9H-purin-9-yl]-5-(5-methyl-1,3,4-oxadiazol-2-yl)tetrahydrofuran-3,4-diol
(2R,3R,4S,5S)-2-[6-(4-chloro-2-fluoroanilino)-9H-purin-9-yl]-5-(3-cyclopropylisoxazol-5-yl)tetrahydrofuran-3,4-diol
(2S,3S,4R,5R)-2-[3-(tert-butyl)isoxazol-5-yl]-5-{6-[(1-butyrylpiperidin-4-yl)amino]-9H-purin-9-yl}tetrahydrofuran-3,4-diol
isopropyl 4-[(9-{(2R,3R,4S,5S)-5-[3-(tert-butyl)isoxazol-5-yl]-3,4-dihydroxytetrahydrofuran-2-yl}-9H-purin-6-yl)amino]piperidine-1-carboxylate
(2S,3S,4R,5R)-2-[3-(tert-butyl)isoxazol-5-yl]-5-(6-{[1-(2,2,2-trifluoroacetyl)piperidin-4-yl]amino}-9H-purin-9-yl)tetrahydrofuran-3,4-diol

methyl 4-[(9-{(2R,3R,4S,5S)-5-[3-(tert-butyl)isoxazol-5-yl]-3,4-dihydroxytetrahydrofuran-2-yl}-9H-purin-6-yl)amino]piperidine-1-carboxylate
(2R,3R,4S,5S)-2-[6-(4-chloro-2-fluoroanilino)-9H-purin-9-yl]-5-[3-(hydroxymethyl)isoxazol-5-yl]tetrahydrofuran-3,4-diol
(2R,3R,4S,5S)-2-[6-(2-chloro-4-fluoroanilino)-9H-purin-9-yl]-5-[3-(hydroxymethyl)isoxazol-5-yl]tetrahydrofuran-3,4-diol
(2R,3R,4S,5S)-2-[6-(2-fluoroanilino)-9H-purin-9-yl]-5-[3-(hydroxymethyl)isoxazol-5-yl]tetrahydrofuran-3,4-diol
(2R,3R,4S,5S)-2-[6-(2-chloroanilino)-9H-purin-9-yl]-5-[3-(hydroxymethyl)isoxazol-5-yl]tetrahydrofuran-3,4-diol
(2R,3R,4S,5S)-2-(2-chloro-6-{[(1S,2S)-2-hydroxycyclopentyl]amino}-9H-purin-9-yl)-5-[3-(hydroxymethyl)isoxazol-5-yl]tetrahydrofuran-3,4-diol
(2R,3R,4S,5S)-2-[2-chloro-6-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl]-5-[3-(hydroxymethyl)isoxazol-5-yl]tetrahydrofuran-3,4-diol
2-[(2-chloro-9-{(2R,3R,4S,5S)-3,4-dihydroxy-5-[3-(hydroxymethyl)isoxazol-5-yl]tetrahydrofuran-2-yl}-9H-purin-6-yl)amino]-N-ethylethanesulfonamide
ethyl 4-[(2-chloro-9-{(2R,3R,4S,5S)-3,4-dihydroxy-5-[3-(hydroxymethyl)isoxazol-5-yl]tetrahydrofuran-2-yl}-9H-purin-6-yl)amino]piperidine-1-carboxylate
(2R,3R,4S,5S)-2-[2-chloro-6-(4-chloro-2-fluoroanilino)-9H-purin-9-yl]-5-[3-(hydroxymethyl)isoxazol-5-yl]tetrahydrofuran-3,4-diol
(2R,3R,4S,5S)-2-[2-chloro-6-(2-chloro-4-fluoroanilino)-9H-purin-9-yl]-5-[3-(hydroxymethyl)isoxazol-5-yl]tetrahydrofuran-3,4-diol
(2R,3R,4S,5S)-2-[2-chloro-6-(2-fluoroanilino)-9H-purin-9-yl]-5-[3-(hydroxymethyl)isoxazol-5-yl]tetrahydrofuran-3,4-diol
(2S,3S,4R,5R)-2-(3-ethylisoxazol-5-yl)-5-[2-methoxy-6-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol
ethyl 4-({9-[(2R,3R,4S,5S)-5-(3-ethylisoxazol-5-yl)-3,4-dihydroxytetrahydrofuran-2-yl]-2-methoxy-9H-purin-6-yl}amino)piperidine-1-carboxylate
(2S,3S,4R,5R)-2-(3-ethylisoxazol-5-yl)-5-(6-{[(1S,2S)-2-hydroxycyclopentyl]amino}-2-methoxy-9H-purin-9-yl)tetrahydrofuran-3,4-diol
(2S,3S,4R,5R)-2-(3-ethylisoxazol-5-yl)-5-(6-{[2-(ethylsulfonyl)ethyl]amino}-2-methoxy-9H-purin-9-yl)tetrahydrofuran-3,4-diol
(2R,3R,4S,5S)-2-[6-(2-chloro-4-fluoroanilino)-2-methoxy-9H-purin-9-yl]-5-(3-ethylisoxazol-5-yl)tetrahydrofuran-3,4-diol

(2S,3S,4R,5R)-2-(3-ethylisoxazol-5-yl)-5-[6-(2-fluoroanilino)-2-methoxy-9H-purin-9-yl]tetrahydrofuran-3,4-diol
(2R,3R,4S,5S)-2-[6-(4-chloro-2-fluoroanilino)-2-methoxy-9H-purin-9-yl]-5-(3-ethylisoxazol-5-yl)tetrahydrofuran-3,4-diol
(2S,3S,4R,5R)-2-[3-(tert-butyl)-1,2,4-oxadiazol-5-yl]-5-[6-(cyclopropylamino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol
(2S,3S,4R,5R)-2-[5-(tert-butyl)-1,3,4-oxadiazol-2-yl]-5-[2-chloro-6-(4-chloro-2-fluoroanilino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol
(2R,3R,4S,5S)-2-[6-(4-chloro-2-fluoroanilino)-9H-purin-9-yl]-5-(5-isopropyl-1,3,4-oxadiazol-2-yl)tetrahydrofuran-3,4-diol.

Compounds according to the invention have applicability as inhibitors of lipolysis i.e. they decrease plasma free fatty acid concentrations. The compounds may thus be used in the treatment of hyperlipidaemias. Furthermore, as a consequence of their anti-lipolytic activity, the compounds have the ability to lower elevated blood glucose, insulin and ketone body levels and therefore may be of value in the therapy of diabetes. Since anti-lipolytic agents have hypolipidaemic and hypofibrinogenaemic activity, the compounds may also show anti-atherosclerotic activity. The anti-lipolytic activity of compounds of the invention has been demonstrated by their ability to lower the concentration of non-esterified fatty acids (NEFA) in starved rats dosed orally according to the method described by P. Strong et al. In Clinical Science (1993), 84, 663-669.

In addition to their anti-lipolytic effect, the compounds of the invention may independently affect cardiac function by reducing heart rate and conduction. The compounds may thus be used in the therapy of a number of cardiovascular disorders, for example cardiac arrythmias, particularly following myocardial infarction, and angina.

Furthermore, the compounds of the invention are useful as cardioprotective agents, having applicability in the treatment of ischaemic heart disease. As used

herein the term "ischaemic heart disease" includes damage associated with both myocardial ischaemia and reperfusion, for example, associated with coronary artery bypass grafting (CABG), percutaneous translumenal coronary angioplasty (PTCA), cardioplegia, acute myocardial infarction, thrombolysis, stable and unstable angina and cardiac surgery including in particular cardiac transplantation. The compounds of the invention additionally are useful for treating ischaemic damage to other organs. The compounds of the invention may also be valuable in the treatment of other disorders arising as a result of widespread atheromatous disease, for example, peripheral vascular disease (PVD) and stroke.

The compounds may also inhibit renin release and thus be of use in the therapy of hypertension and heart failure. The compounds may also be useful as CNS agents (e.g. as hypnotics, sedatives, analgesics and/or anti-convulsants particularly finding use in the treatment of epilepsy).

In addition, the compounds of the invention may find use in the treatment of sleep apnoea.

The compound of formula (I) and pharmaceutically acceptable acid addition salts thereof are useful as analgesics. They are therefore useful in treating or preventing pain. They may be used to improve the condition of a host, typically of a human being, suffering from pain. They may be employed to alleviate pain in a host. Thus, the compound of formula (I) and its pharmaceutically acceptable acid addition salts may be used as a preemptive analgesic to treat acute pain such as musculoskeletal pain, post operative pain and surgical pain, chronic pain such as chronic inflammatory pain (e.g. rheumatoid arthritis (RA) and osteoarthritis (OA), neuropathic pain (e.g. post herpetic neuralgia (PHN), trigeminal neuralgia, neuropathies associated with diabetes and sympathetically maintained pain) and pain associated with cancer and fibromyalgia. The compound of formula (I) may also be used in the treatment or prevention of pain associated with migraine, tension headache and cluster headaches and pain associated with Functional Bowel Disorders (e.g. Irritable Bowel Syndrome), non cardiac chest pain and non ulcer dyspepsia.

Additionally, when topically administered, the compounds of the present invention exhibit analgesic and anti-inflammatory activity and are therefore useful in a number of chronic inflammatory pain conditions such as OA, RA and neuropathic conditions such as fibomyalgia and PHN.

Accordingly, the invention provides a compound of formula (I) or a physiologically acceptable salt or solvate thereof for use in therapy, and in particular in the treatment of human or animal subjects suffering from a condition in which there is an advantage in decreasing plasma free fatty acid concentration, or reducing heart rate and conduction, or whereby the therapy involves the treatment of ischaemic heart disease, peripheral vascular disease or stroke or which subject is suffering from a CNS disorder, sleep apnoea or pain.

In a further aspect, the invention provides a method of treatment of a human or animal subject suffering from a condition in which there is an advantage in decreasing plasma free fatty acid concentration, or reducing heart rate and conduction, or which subject is suffering from or susceptible to ischaemic heart disease, peripheral vascular disease or stroke, or which subject is suffering a CNS disorder or suffering from sleep apnoea or suffering pain, which method comprises administering to the subject an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof.

In a further aspect, the invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof for the manufacture of a medicament for the treatment of a human or animal suffering from a condition in which there is an advantage in decreasing plasma free fatty acid concentration, or reducing heart rate and conduction, or which subject is suffering from or susceptible to ishaemic heart disease, peripheral vascular disease or stroke, or which subject is suffering a CNS disorder or suffering from sleep apnoea or suffering pain.

In respect of the above mentioned ischaemic treatment, it has been found that according to a particularly unexpected aspect of the present invention, not only does administration of a compound of formula (I) prior to ischaemia provide

protection against myocardial infarction, but protection is also afforded if the compound of formula (I) is administered after the ischaemic event and before reperfusion. This means that the methods of the present invention are applicable not only where ischaemia is planned or expected, for example in cardiac surgery, but also in cases of sudden or unexpected ischaemia, for example in heart attack and unstable angina.

It will be appreciated that reference to treatment includes acute treatment or prophylaxis as well as the alleviation of established symptoms.

The pharmaceutical composition comprises, as active ingredient, at least one compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof in association with a pharmaceutical carrier and/or excipient for use in therapy, and in particular in the treatment of human or animal subjects suffering from a condition in which there is an advantage in decreasing plasma free fatty acid concentration, or reducing heart rate and conduction, or which subject is suffering from or susceptible to ischaemic heart disease, peripheral vascular disease or stroke, or which subject is suffering from a CNS disorder, sleep apnoea or pain.

There is further provided by the present invention a process of preparing a pharmaceutical composition, which process comprises mixing at least one compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, together with a pharmaceutically acceptable carrier and/or excipient.

Compositions according to the invention may be formulated for topical, oral, buccal, parenteral or rectal administration or in a form suitable for administration by inhalation or insufflation. Oral administration is preferred. The compositions may be adapted for sustained release.

For topical administration, the pharmaceutical composition may be given in the form of a transdermal patch.

Tablets and capsules for oral administration may contain conventional excipients such as binding agents, for example mucilage of starch or

polyvinylpyrrolidone; fillers, for example, lactose, microcrystalline cellulose or maize-starch; lubricants, for example, magnesium stearate or stearic acid; disintegrants, for example, potato starch, croscarmellose sodium or sodium starch glycollate; or wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in the art. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example, sorbitol syrup, methyl cellulose, or carboxymethyl cellulose; emulsifying agents, for example, sorbitan mono-oleate; non-aqueous vehicles (which may include edible oils), for example, propylene glycol or ethyl alcohol; and preservatives, for example, methyl or propyl p-hydroxybenzoates or sorbic acid. The preparations may also contain buffer salts, flavouring, colouring and sweetening agents (e.g. mannitol) as appropriate.

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

The compounds of formula (I) may be formulated for parenteral administration by bolus injection or continuous infusion and may be presented in unit dose form in ampoules, or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

The compounds of formula (I) may also be formulated as suppositories, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

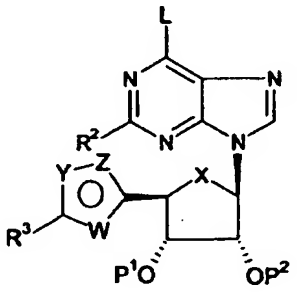
A proposed dose of the compounds of the invention for administration to man (of approximately 70kg body weight) is 1mg to 2g, preferably 1mg to 100mg, of the active ingredient per unit dose which could be administered, for example, 1

to 4 times per day. It will be appreciated that it may be necessary to make routine variations to the dosage, depending on the age and condition of the patient. The dosage will also depend on the route of administration.

In a yet further aspect the invention also provides for the use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof for the manufacture of a medicament for the treatment of human or animal subjects suffering from a condition in which there is an advantage in decreasing plasma free fatty acid concentration, or reducing heart rate and conduction, or which subject is suffering from or susceptible to ischaemic heart disease, peripheral vascular disease (PVD) or stroke, or which patient is suffering from a CNS disorder, sleep apnoea or pain.

The compounds of formula (I) and physiologically acceptable salts or solvates thereof may be prepared by the processes described hereinafter, said processes constituting a further aspect of the invention. In the following description, the groups R^1, R^2 and R^3 are as defined for compounds of formula (I) unless otherwise stated.

According to a first general process A, a compound of formula (I) may be prepared by reacting a compound of formula (II)



(II)

wherein L represents a leaving group such as a halogen atom (e.g. chlorine), or a linker group capable of binding to a solid phase polymeric support (e.g. a polystyrene resin) and for example may be $-SO_2C_{1-4}$alkylene and P^1 and P^2 represent hydrogen, C_{1-6} straight chain or branched alkyl or a suitable protecting group (e.g. acetyl or a protecting group wherein P^1 and P^2 together form an

alkylidine group) with a compound of formula R^1NH_2 or a salt thereof under basic conditions. The 4'-heterocycle group substituent may be protected if required, for example, see route Bb and V described hereinbelow.

Compounds of formula (II) may be used to produce compounds of formula (I) directly by reaction with the group R^1NH_2 either in the absence or presence of a solvent such as an alcohol (e.g. a lower alkanol such as isopropanol, t-butanol or 3-pentanol), an ether (e.g. tetrahydrofuran or dioxan), a substituted amide (e.g. dimethylformamide), a halogenated hydrocarbon (e.g. chloroform), an aromatic hydrocarbon (e.g. toluene), dimethyl sulfoxide (DMSO) or acetonitrile, preferably at an elevated temperature (e.g. up to the reflux temperature of the solvent), in the presence of a suitable acid scavanger, for example, inorganic bases such as sodium, cesium or potassium carbonate, or organic bases such as triethylamine, diisopropylethylamine or pyridine, optionally in the presence of a palladium catalyst (e.g. palladium acetate) and phosphine ligand (e.g. R-(+)-2,2'-bis(diphenylphosphino)-1-1' binaphthyl).

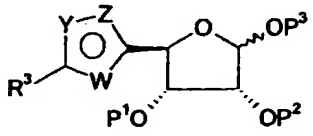
Optionally, where at least one of Y, Z and W is N, alkylation may be carried out on a N atom at Y, Z or W at any appropriate stage in the synthesis, for example, see Route X described hereinbelow.

The above reactions may be preceded or followed where appropriate by in situ removal of the P^1 and P^2 protecting groups. For example when P^1 and P^2 represent acetyl, this may be effected with an amine such as ammonia or tert-butylamine in a solvent such as methanol or when P^1 and P^2 represent an alkylidine by acid hydrolysis, e.g. with trifluoroacetic acid (TFA). Interconversion of P^1 and P^2 protecting groups may occur at any stage in the preparation of the compounds of formula (II), for example when P^1 and P^2 represent acetyl, compounds of formula (II) may be prepared from compounds wherein P^1 and P^2 together represent an alkylidine protecting group by acid catalysed removal of the alkylidine protecting group, e.g. with hydrogen chloride in methanol followed by in situ acylation, for example with acetic anhydride in the presence of a base such as pyridine, in a solvent such as dichloromethane.

Otherwise, interconversion of P^1 and P^2 protecting groups may occur at any stage during the preparation of compounds of formula (II).

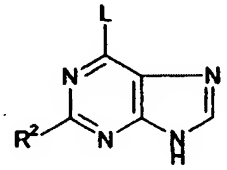
It will be apparent to persons skilled in the art that in the preparation of compounds of formula (II) or (I) the 4'-heterocycle may be formed at any stage. For example, heterocycles may be prepared from carboxylic acid or acetylene starting materials before the addition of the purine ring (see Schemes 1, 1a and 2) or heterocycles may be formed after the addition of the purine ring (see Schemes 3, 4 and 5 and Route W).

Compounds of formula (II) where X = O may be prepared by reacting compounds of formula (III)



(III)

wherein P^3 represents a suitable protecting group, for example acetyl, or a substituent such as C_{1-3} alkyl, and P^1, P^2 and R^3 are as defined above, with compounds of formula (IV)



(IV)

wherein L and R^2 are as defined above.

The reaction is conveniently carried out in a suitable solvent, such as acetonitrile in the presence of a silylating agent such as trimethylsilyl trifluoromethane sulfonate and a base such as diazabicyclo[5.4.0]undec-7-ene (DBU). Alternatively the compound of formula (IV) may first be silylated with a suitable silylating agent e.g. hexamethyldisilazane followed by reaction of the silylated

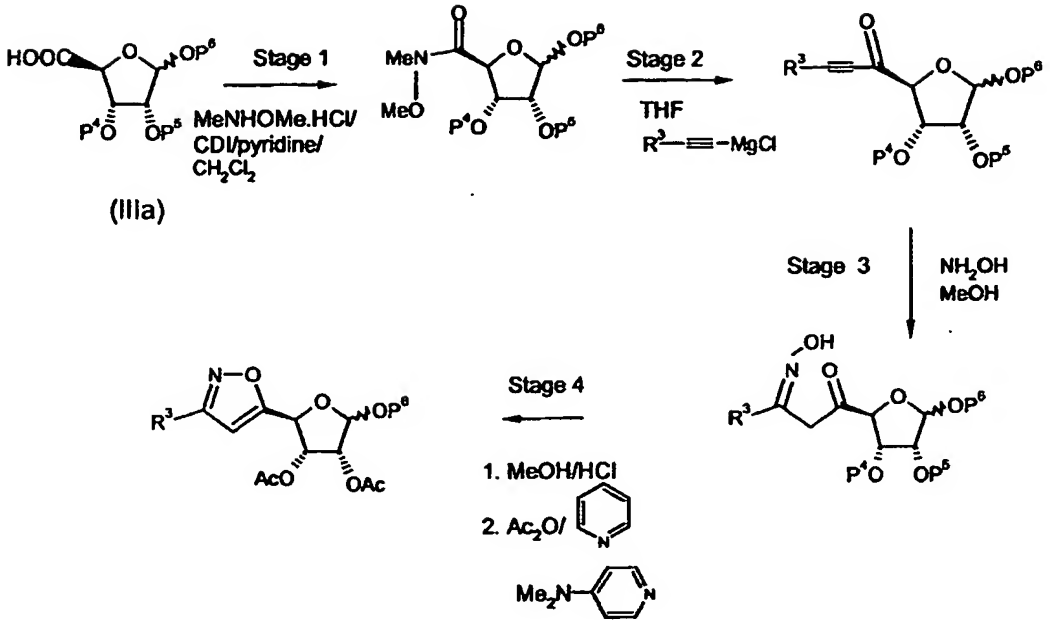
intermediate with a compound of formula (III) and a suitable Lewis acid, e.g. trimethylsilyl trifluoromethanesulfonate in a suitable solvent such as acetonitrile.

Compounds of formula (IV) are either known in the art or may be prepared from known compounds using methods analogous to those used to prepare the known compounds of formula (IV).

As described above, the compounds of formula (III) may be prepared from alternative protected compounds by replacement of the alternate P^1 and P^2 protecting groups with other P^1 and P^2 groups. These represent an exchanging of one protecting group for another and will be apparent to those skilled in the art. Compounds of formula (III) may be made for example by the following syntheses:

Compounds of formula (III) may be prepared, for example when the heterocycle defined by W, Y and Z hereinabove represents an isoxazole (optionally substituted) by the following reaction schemes.

Scheme 1

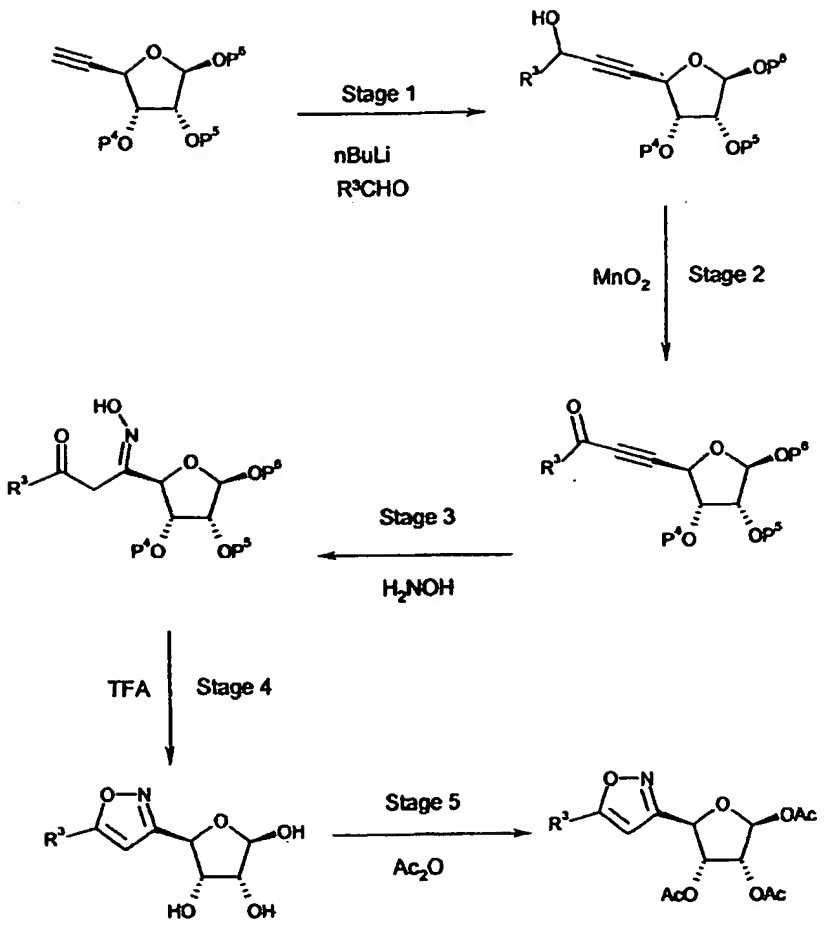


General conditions for Stages 1-4 will be known to persons skilled in the art. It will also be appreciated that the reagents and conditions set out in Scheme 1 are example conditions and alternative reagents and conditions for achieving the same chemical transformation may be known to persons skilled in the art. P^4 and P^5 together represent alkylidine protecting group(s). P^6 represents C_{1-4} alkyl. R^3 is as previously defined.

Although scheme 1 shows the preparation of compounds of formula (III) where the heterocycle moiety is an isoxazole it would be apparent to a person skilled in the art that other standard methods could be employed to produce compounds of formula (III) with other heterocycles from carboxylic acid starting materials, such a compound of formula (IIIa), for example, see route Q as described hereinbelow.

An alternative method for synthesis of compounds of formula (III) is shown in Scheme 1a.

Scheme 1a

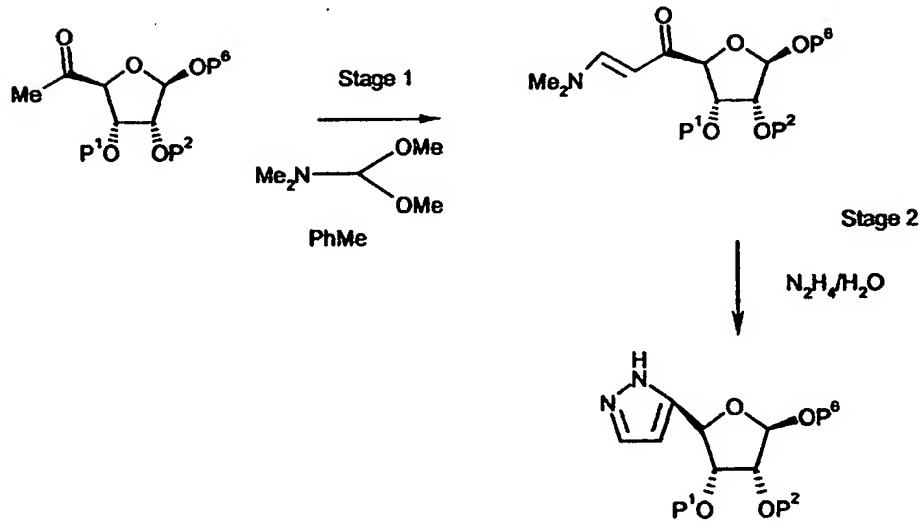

Stage 1
nBuLi
R³CHO
MnO₂
Stage 2
Stage 3
H₂NOH
TFA
Stage 4
Stage 5
Ac₂O

5

General conditions for Stages 1-5 in Scheme 1a will be known to persons skilled in the art. R^3, P^4, P^5 and P^6 are as previously defined.

Scheme 2 represents a method of preparing compounds of formula (III) when Y = N, Z = NH, W = CH and R^3 = H or tautomers thereof. P^1, P^2 and P^6 are as previously defined.

Scheme 2



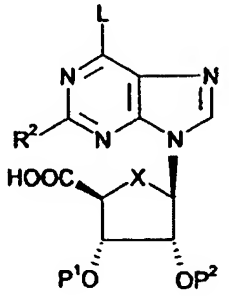
A further process (B) comprises converting a compound of formula (I) into a different compound of formula (I) by modifying the R^1, R^2 and/or R^3 groups therein.

All compounds of formulae (III) are novel intermediates and form a further aspect of the present invention.

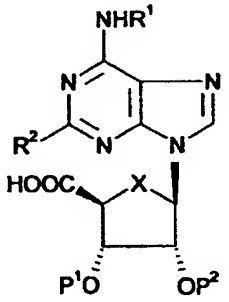
Compounds of the formula R^1NH_2 are either known compounds or may be prepared from known compounds using conventional procedures.

Specific optical isomers of a compound of formula (I) may be obtained by conventional methods for example, by synthesis from an appropriate asymmetric starting material using any of the processes described herein, or where appropriate by separation of a mixture of isomers of a compound of formula (I) by conventional means e.g by fractional crystallisation or chromatography.

According to a third process (C), compounds of formula (I) may be prepared from compounds of formula (V) or (VI):



(V)



(VI)

where R^1, R^2,X, L, P^1 and P^2 represent groups as previously defined.

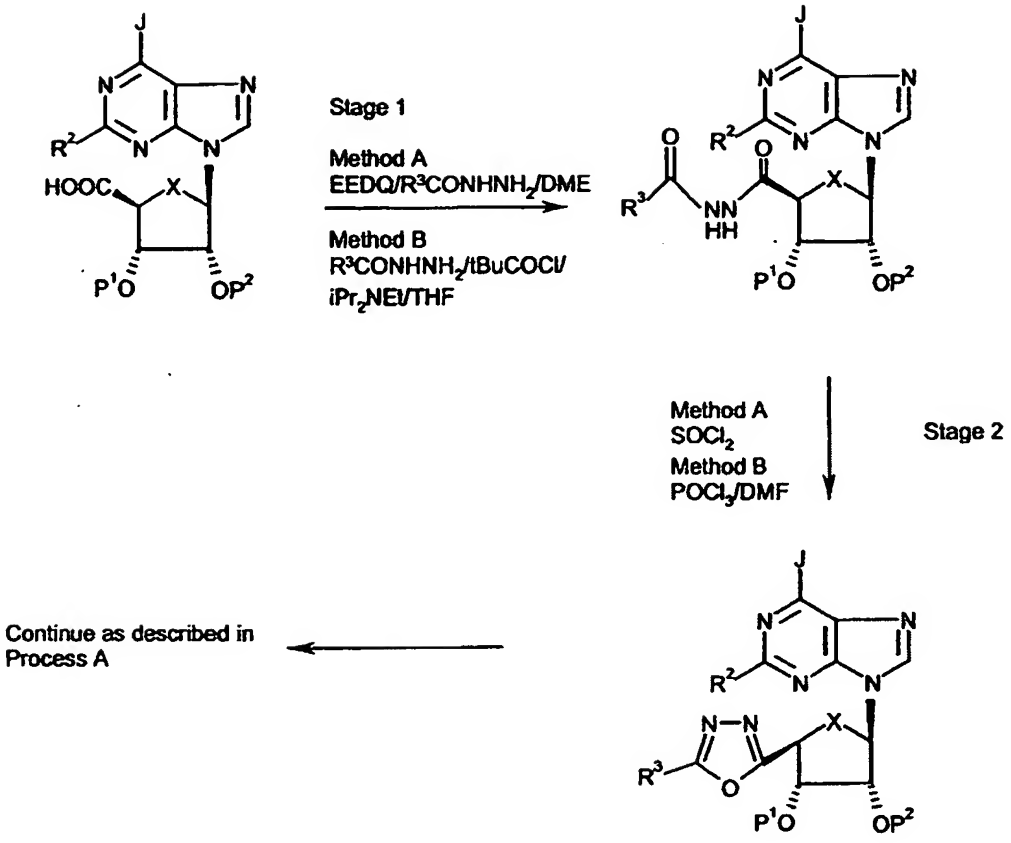
Also compounds of formula (VI) may be prepared from compounds of formula (V) by analogous methods to those described in process (A) above.

Synthesis of the compounds of formulae (I) from the corresponding acids of formulae (V) and (VI) will be apparent to a skilled person using conventional synthetic techniques.

As an example, when W = O, Y = N and Z = N in formula 1 above thus defining a 1,3,4 oxadiazole, the synthesis is according to reaction scheme 3. J represents a leaving group L as previously defined, or a NHR^1 group. R^2, X, P^1 and P^2 are as previously defined.

5

Scheme 3

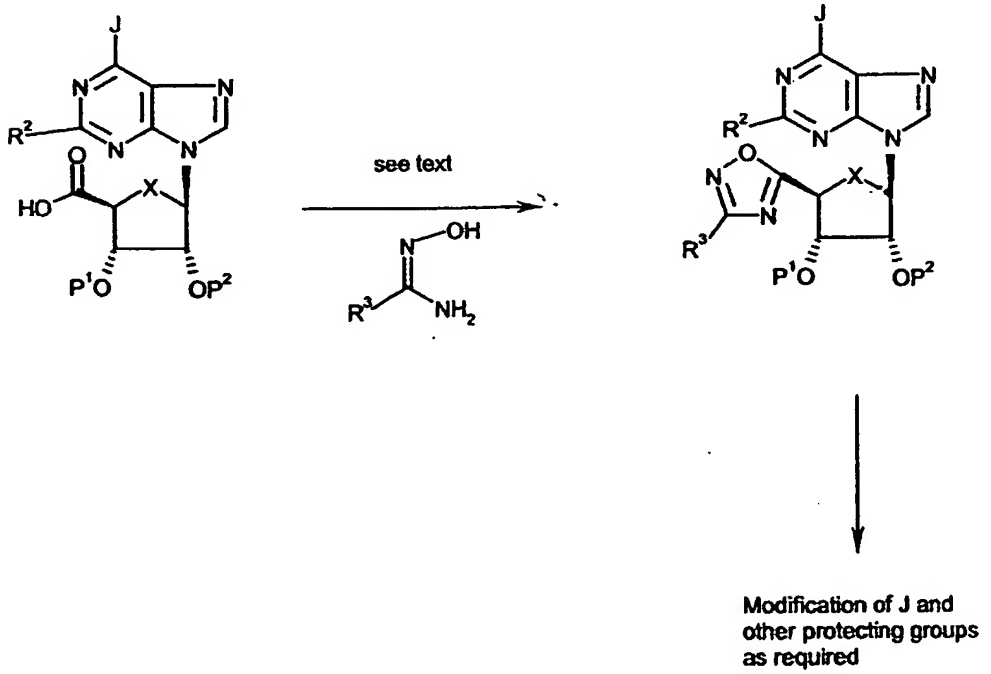


Compounds of formula (I) where Z=O, Y=N and W=N (thus defining a 1,2,4-oxadiazole) may be prepared from compounds of formula (V) or (VI) by a first process involving activation of the carboxyl group on the compound of formula (V) or (VI) followed by reaction with an amidoxime of formula HO-N=C(R^3)NH_2 in a solvent such as tetrahydrofuran or chloroform, in the presence of a base such as pyridine or di-isopropylethylamine, followed by cyclisation at a temperature of 20°C-150°C in a solvent such as toluene, tetrahydrofuran (THF) or chloroform (see scheme 4). Methods of carboxyl activation include reaction with an acid chloride, such as pivaloyl chloride, or an acid anhydride in the presence of a base such as a tertiary amine, for example di-isopropylethylamine, or with thionyl chloride in dimethylformamide (DMF). Activating agents used in peptide

chemistry such as 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ) or 1-hydroxybenzotriazole and 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride, may also be used. Hydroxyl protecting groups may be removed under conditions known to those practising in the art. For example, the acetonide group may be removed by treatment with an acid (at a temperature of 0°C-150°C) such as trifluoroacetic acid suitably at 0-20°C or acetic acid suitably at 50-150°C.

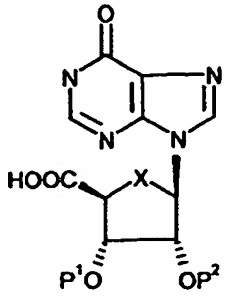
In scheme 4 R^2, R^3, X, J, P^1 and P^2 and are as defined above.

Scheme 4



Alternatively, a compound of formula (II) may be prepared from a compound of formula (VII), for example, see route U as described hereinbelow. It would be apparent to persons skilled in the art that analagous methods to route U could

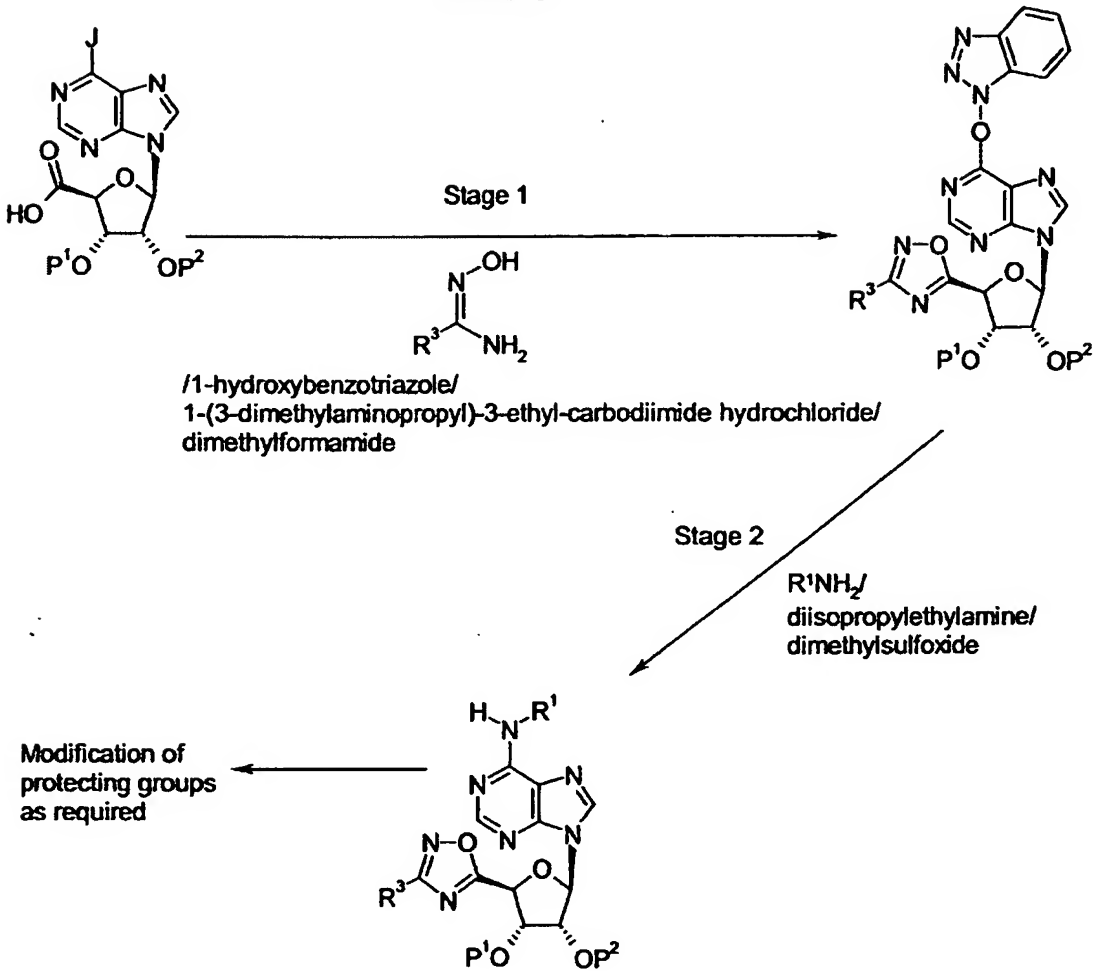
be used to prepare compounds of formula (I) with other 4'-heterocycles, for example, see route M as described hereinbelow.



(VII)

According to an general process D, a compound of formula (I) may be prepared from a compound of formula (V), as shown in Scheme 5, followed by removal of the P^1 and P^2 protecting groups as described previously in process A. It will be apparent to persons skilled in the art that analagous methods to that shown in Scheme 5 could be used to prepare compounds of formula (I) with other 4'-heterocycles using alternative heterocycle syntheses. In Scheme 5, R^1, R^3, J, P^1 and P^2 are as previously defined.

Scheme 5



The invention is further illustrated by the following non limiting intermediates and Examples.

Full experimental details are given below for routes A-Z, Bb and Cc; data for remaining examples prepared by analogous routes are given in Table 1.

Standard HPLC conditions are as follows:

Standard Automated Preparative HPLC column, conditions & eluent

Automated preparative high performance liquid chromatography (autoprep. HPLC) was carried out using a Supelco ABZ+ 5 m 100mmx22mm i.d. column eluted with a mixture of solvents consisting of I) 0.1% formic acid in water and ii) 0.05% formic acid in acetonitrile, the eluent being expressed as the percentage of ii) in the solvent mixture, at a flow rate of 4ml per minute. Unless otherwise stated the eluent was used as a gradient of 0-95 % (ii) over 18.5 minutes.

LC/MS System

Four alternative Liquid Chromatography Mass Spectroscopy (LC/MS) systems were used:

System A:
This system used an ABZ+PLUS, 3.3cm x 4.6mm i.d. column, eluting with solvents: A – 0.1%v/v formic acid + 0.077%w/v ammonium acetate in water; and B – 95:5 acetonitrile:water + 0.05%v/v formic acid, at a flow rate of 1ml per minute. The following gradient protocol was used: 100% A for 0.7 mins; A+B mixtures, gradient profile 0 – 100% B over 3.5mins; hold at 100% B for 3.5mins; return to 100% A over 0.3mins.

System B:
This system used an ABZ+PLUS, 3.3cm x 2.0mm i.d. column, eluting with solvents: A – 0.1%v/v formic acid + 0.077%w/v ammonium acetate in water; and B – 95:5 acetonitrile:water + 0.05%v/v formic acid, at a flow rate of 0.8ml per minute. The following gradient protocol was used: A+B mixtures, gradient profile 0 – 100% B over 3.5mins; hold at 100% B for 1.5mins; return to 100% A over 0.5mins.

System C:
This system used an ABZ+PLUS, 3.3cm x 4.6mm i.d. column, eluting with solvents: A – 0.1%v/v formic acid + 0.077%w/v ammonium acetate in water;

and B – 95% acetonitrile:water + 0.05%v/v formic acid, at a flow rate of 3ml per minute. The following gradient protocol was used: 100% A for 0.7 mins; A+B mixtures, gradient profile 0 – 100% B over 3.7mins; hold at 100% B for 0.9mins; return to 100% A over 0.2mins.

System D:

This system used an ABZ+PLUS, 3.3cm x 4.6mm i.d. column, eluting with solvents: A – 0.1%v/v formic acid in water; and B – 95% acetonitrile:water + 0.07%v/v formic acid, at a flow rate of 1.5ml per minute. The following gradient protocol was used: 100% A for 0.2 mins; A+B mixtures, gradient profile 0 – 100% B over 3.3mins; hold at 100% B for 1min; return to 100% A over 0.2mins.

All LC/MS systems used a micromass 'platform' spectrometer, with electrospray ionisation mode, positive and negative ion switching, mass range 80-1000 a.m.u.

Flash chromatography was carried out either on Merck silica gel (Merck 9385), or on pre-packed silica gel cartridges (Biotage).

All temperatures were in °C.

Examples Table.

Table 1. Examples

Ex No	Name	Expt. Details (note 1)	Characterising data
1	(2R,3R,4S,5S)-2-[6-(2R-Hydroxy-cyclopent-(R)-ylamino)-purin-9-yl]-5-(5-isopropyl-[1,3,4]oxadiazol-2-yl)-tetrahydro-furan-3,4-diol	Analogous method to route A	TLC SiO_2 (CH_2Cl_2:MeOH: 880NH_3 90:10:1) R_f = 0.39 Microanalysis Found: C,52.9; H, 5.9; N, 22.7. $C_{19}H_{23}N_7O_5$ requires C, 52.9; H, 5.8; N, 22.7.

Table 1. Examples			
Ex No	**Name**	**Expt. Details (note 1)**	**Characterising data**
2	(2R,3R,4S,5S)-2-(6-Cyclopentylamino-purin-9-yl)-5-(5-phenyl-[1,3,4]oxadiazol-2-yl)-tetrahydro-furan-3,4-diol	Analogous method to route A	TLC SiO_2 (CH_2Cl_2:MeOH: 880NH_3 94:6:1) R_f = 0.10 Microanalysis Found: C,57.1; H, 5.3; N, 21.0. $C_{22}H_{23}N_7O_4$ requires C, 57.2; H, 5.3; N, 21.2.
3	(2S,3S,4R,5R)-2-(5-tert-Butyl-[1,3,4]oxadiazol-2-yl)-5-[6-(tetrahydro-pyran-4-ylamino)-purin-9-yl]-tetrahydro-furan-3,4-diol	See below (route A)	See below (route A)
4	4-{9-[5S-(5-tert-Butyl-[1,3,4]oxadiazol-2-yl)-3R,4S-dihydroxy-tetrahydro-furan-2R-yl]-9H-purin-6-ylamino}-piperidine-1-carboxylic acid ethyl ester	Analogous method to route A	LC/MS (System B) R_t 2.55 min. Mass Spectrum *m/z* 517 [MH^+].
5	(2S,3S,4R,5R)-2-(5-tert-Butyl-[1,3,4]oxadiazol-2-yl)-5-[6-(2S-hydroxy-cyclopent-(S)-ylamino)-purin-9-yl]-tetrahydro-furan-3,4-diol	Analogous method to route A	LC/MS (System B) R_t 2.35 min. Mass Spectrum *m/z* 446 [MH^+].
6	(2S,3S,4R,5R)-2-(5-Isopropyl-[1,3,4]oxadiazol-2-yl)-5-[6-(tetrahydro-pyran-4-ylamino)-purin-9-yl]-tetrahydro-furan-3,4-diol	Analogous method to route A	LC/MS (System B) R_t 2.24 min. Mass Spectrum *m/z* 432 [MH^+].

Table 1. Examples			
Ex No	**Name**	**Expt. Details (note 1)**	**Characterising data**
7	(2S,3S,4R,5R)-2-(5-tert-Butyl-[1,3,4]oxadiazol-2-yl)-5-(6-cyclopentylamino-purin-9-yl)-tetrahydro-furan-3,4-diol	Analogous method to route A	LC/MS (System B) R_t 2.61 min. Mass Spectrum *m/z* 430 [MH^+].
8	(2S,3S,4R,5R)-2-(5-tert-Butyl-[1,3,4]oxadiazol-2-yl)-5-[2-chloro-6-(tetrahydro-pyran-4-ylamino)-purin-9-yl]-tetrahydro-furan-3,4-diol formate	See below (route B)	See below (route B)
9	(2S,3S,4R,5R)-2-(5-tert-Butyl-[1,3,4]oxadiazol-2-yl)-5-(2-chloro-6-cyclopentylamino-purin-9-yl)-tetrahydro-furan-3,4-diol formate	Analogous method to route B	LC/MS (System A) R_t 4.35 min. Mass Spectrum *m/z* 464 [MH^+].
10	(2S,3S,4R,5R)-2-(5-Cyclopropyl-[1,3,4]oxadiazol-2-yl)-5-[6-(2S-hydroxy-cyclopent-(S)-ylamino)-purin-9-yl]-tetrahydro-furan-3,4-diol	Analogous method to route A	LC/MS (System D) R_t 2.32 min. Mass Spectrum *m/z* 430 [MH^+].
11	(2R,3R,4S,5S)-2-(6-Cyclopentylamino-purin-9-yl)-5-(5-cyclopropyl-[1,3,4]oxadiazol-2-yl)-tetrahydro-furan-3,4-diol	Analogous method to route A	LC/MS (System D) R_t 2.44 min. Mass Spectrum *m/z* 414 [MH^+].

Table 1. Examples			
Ex No	Name	Expt. Details (note 1)	Characterising data
12	4-{9-[5S-(5-Cyclopropyl-[1,3,4]oxadiazol-2-yl)-3R,4S-dihydroxy-tetrahydro-furan-2R-yl]-9H-purin-6-ylamino}-piperidine-1-carboxylic acid ethyl ester	Analogous method to route A	LC/MS (System D) R_t 2.57 min. Mass Spectrum *m/z* 501 [MH^+].
13	(2R,3R,4S,5S)-2-(6-Cyclopentylamino-purin-9-yl)-5-(5-cyclopentyl-[1,3,4]oxadiazol-2-yl)-tetrahydro-furan-3,4-diol	Analogous method to route A	LC/MS (System D) R_t 2.74 min. Mass Spectrum *m/z* 442 [MH^+].
14	(2S,3S,4R,5R)-2-(5-tert-Butyl-[1,3,4]oxadiazol-2-yl)-5-[6-(4-chloro-2-fluoro-phenylamino)-purin-9-yl]-tetrahydro-furan-3,4-diol	Analogous method to route A	LC/MS (System B) R_t 2.99 min. Mass Spectrum *m/z* 490 [MH^+].
15	(2R,3R,4S,5S)-2-(6-Cyclopentylamino-purin-9-yl)-5-[1,3,4]oxadiazol-2-yl-tetrahydro-furan-3,4-diol	See below (route C)	See below (route C)
16	(2S,3S,4R,5R)-2-(5-Ethyl-oxazol-2-yl)-5-[6-(tetrahydro-pyran-4-ylamino)-purin-9-yl]-tetrahydro-furan-3,4-diol	See below (route D)	See below (route D)
17	(2S,3S,4R,5R)-2-(6-Cyclopentylamino-purin-9-yl)-5-(5-cyclopropyl-[1,3,4]thiadiazol-2-yl)-tetrahydro-furan-3,4-diol	See below (route E)	See below (route E)

Table 1. Examples			
Ex No	Name	Expt. Details (note 1)	Characterising data
18	(2R,3R,4S,5R)-2-(6-Isopropylamino-purin-9-yl)-5-(5-methyl-4H-[1,2,4]triazol-3-yl)-tetrahydro-furan-3,4-diol trifluoroacetate	See below (route F)	See below (route F)
19	(2S,3S,4R,5R)-2-(3-Cyclopropyl-[1,2,4]oxadiazol-5-yl)-5-[6-(2S-hydroxy-cyclopent-(S)-ylamino)-purin-9-yl]-tetrahydro-furan-3,4-diol	See below (route G)	LC/MS (System B) R_t 2.37 min. Mass Spectrum *m/z* 430 [MH^+].
20	(2S,3S,4R,5R)-2-(3-Phenyl-[1,2,4]oxadiazol-5-yl)-5-[6-(tetrahydro-pyran-4-ylamino)-purin-9-yl]-tetrahydro-furan-3,4-diol	Analogous method to route G	TLC SiO_2 (CH_2Cl_2:EtOH: 880NH_3) 100:8:1 R_f = 0.5 Microanalysis Found: C,54.8; H, 4.9; N, 20. Requires C, 55.3; H, 5.3; N, 19.6.
21	(2S,3S,4R,5R)-2-(3-tert-Butyl-[1,2,4]oxadiazol-5-yl)-5-[6-(2S-hydroxy-cyclopent-(S)-ylamino)-purin-9-yl]-tetrahydro-furan-3,4-diol	Analogous method to route G	LC/MS (System B) R_t 2.57 min. Mass Spectrum *m/z* 446 [MH^+].

Table 1. Examples			
Ex No	Name	Expt. Details (note 1)	Characterising data
22	(2S,3S,4R,5R)-2-(3-Cyclopropyl-[1,2,4]oxadiazol-5-yl)-5-[6-(tetrahydro-pyran-4-ylamino)-purin-9-yl]-tetrahydro-furan-3,4-diol	Analogous method to route G	LC/MS (System B) R_t 2.39 min. Mass Spectrum *m/z* 430 [MH^+].
23	(2R,3R,4S,5S)-2-[6-(Tetrahydro-pyran-4-ylamino)-purin-9-yl]-5-(3-thiazol-5-yl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol	Analogous method to route G	LC/MS (System B) R_t 2.29 min. Mass Spectrum *m/z* 473 [MH^+].
24	(2S,3S,4R,5R)-2-(3-Methyl-[1,2,4]oxadiazol-5-yl)-5-[6-(tetrahydro-pyran-4-ylamino)-purin-9-yl]-tetrahydro-furan-3,4-diol	Analogous method to route G	^{1}HNMR δ (DMSO) 8.42 (1H,s,CH), 8.20 (1H,brs,CH), 7.82 (1H,brd,NH), 6.18 (1H,d,CH), 6.02 (1H,brd,OH), 5.90 (1H,brd,OH), 5.22 (1H,d,CH), 4.38 (1H,brs,CH), 3.94 (2H,brd,2xCH equatorial), 3.42 (2H,t,2xCH axial), 2.40 (3H,s,CH_3), 1.90-1.60 (4H,2xm,2xCH_2). Microanalysis Found: C, 50.6; H, 5.2; N, 24.3. Requires C, 50.6; H, 5.25; N, 24.3.

Table 1. Examples			
Ex No	Name	Expt. Details (note 1)	Characterising data
25	(2R,3R,4S,5S)-2-[6-(3-Fluoro-4-hydroxy-phenylamino)-purin-9-yl]-5-(3-methyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol	Analogous method to route G	LC/MS (System C) R_t 2.53 min. Mass Spectrum *m/z* 430 [MH^+].
26	4-{9-[5R-(5-tert-Butyl-[1,2,4]oxadiazol-3-yl)-3R,4S-dihydroxy-tetrahydro-furan-2R-yl]-9H-purin-6-ylamino}-piperidine-1-carboxylic acid ethyl ester	See below (route H)	LC/MS (System B) R_t 2.76 min. Mass Spectrum *m/z* 517 [MH^+].
27	(2S,3S,4R,5R)-2-(3-tert-Butyl-isoxazol-5-yl)-5-[6-(2S-hydroxy-cyclopent-(S)-ylamino)-purin-9-yl]-tetrahydro-furan-3,4-diol	See below (route I)	See below (route I)
28	(2S,3S,4R,5R)-2-(3-tert-Butyl-isoxazol-5-yl)-5-[6-(tetrahydro-pyran-4-ylamino)-purin-9-yl]-tetrahydro-furan-3,4-diol	See below (route I)	See below (route I)
29	(2R,3R,4S,5R)-2-(2H-Pyrazol-3-yl)-5-(6-tetrahydro-pyran-4-ylamino-purin-9-yl)-tetrahydro-furan-3,4-diol	See below (route J)	See below (route J)

Table 1. Examples			
Ex No	Name	Expt. Details (note 1)	Characterising data
30	(2R,3R,4S,5R)-2-(5-tert-Butyl-2H-pyrazol-3-yl)-5-(6-cyclopentylamino-purin-9-yl)-tetrahydro-furan-3,4-diol	See below (route K)	See below (route K)
31	(2R,3R,4S,5S)-2-[6-(1S-hydroxymethyl-2-phenyl-ethylamino)-2-methoxy-purin-9-yl]-5-(3-ethyl-isoxazol-5-yl)-tetrahydro-furan-3,4-diol	See below (route L)	See below (route L)
32	(1S,2R,3S,5R)-3-(3-Cyclopropyl-[1,2,4]oxadiazol-5-yl)-5-[2S-hydroxy-cyclopent-(S)-ylamino)-purin-9-yl]-cyclopentane-1,2-diol	See below (route M)	See below (route M)
33	(2R,3R,4S,5S)-2-[6-(tert-butylamino)-9H-purin-9-yl]-5-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)tetrahydrofuran-3,4-diol	Analogous method to route G	LC/ MS (System C) R_t 2.91 min. Mass Spectrum *m/z* 402 [MH^+].
34	(2S,3S,4R,5R)-2-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-5-[6-(isopropylamino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol	Analogous method to route G	LC/ MS (System C) R_t 2.54 min. Mass Spectrum *m/z* 388 [MH^+].

Table 1. Examples			
Ex No	Name	Expt. Details (note 1)	Characterising data
35	(2R,3R,4S,5S)-2-(6-{[(1R,2R)-2-hydroxycyclopentyl]amino}-9H-purin-9-yl)-5-(3-methyl-1,2,4-oxadiazol-5-yl)tetrahydrofuran-3,4-diol	Analogous method to route G	LC/ MS (System C) R_t 2.32 min. Mass Spectrum *m/z* 404 [MH^+].
36	(2S,3S,4R,5R)-2-(3-methyl-1,2,4-oxadiazol-5-yl)-5-[6-(tetrahydro-2H-thiopyran-4-ylamino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol	Analogous method to route G	LC/ MS (System C) R_t 2.54 min. Mass Spectrum *m/z* 420 [MH^+].
37	ethyl 4-({9-[(2R,3R,4S,5S)-3,4-dihydroxy-5-(3-methyl-1,2,4-oxadiazol-5-yl)tetrahydrofuran-2-yl]-9H-purin-6-yl}amino)piperidine-1-carboxylate	Analogous method to route G	LC/ MS (System C) R_t 2.56 min. Mass Spectrum *m/z* 475 [MH^+].
38	(2R,3R,4S,5S)-2-[6-(isobutylamino)-9H-purin-9-yl]-5-(3-methyl-1,2,4-oxadiazol-5-yl)tetrahydrofuran-3,4-diol	Analogous method to route G	LC/ MS (System C) R_t 2.51 min. Mass Spectrum *m/z* 376 [MH^+].
39	(2R,3R,4S,5S)-2-[6-(cyclopentylamino)-9H-purin-9-yl]-5-(3-methyl-1,2,4-oxadiazol-5-yl)tetrahydrofuran-3,4-diol	Analogous method to route G	LC/ MS (System C) R_t 2.47 min. Mass Spectrum *m/z* 388 [MH^+].

Table 1. Examples			
Ex No	Name	Expt. Details (note 1)	Characterising data
40	(2R,3R,4S,5S)-2-{6-[(cyclopropylmethyl)amino]-9H-purin-9-yl}-5-(3-methyl-1,2,4-oxadiazol-5-yl)tetrahydrofuran-3,4-diol	Analogous method to route G	LC/ MS (System C) R_t 2.41 min. Mass Spectrum *m/z* 374 [MH^+].
41	(2R,3R,4S,5S)-2-[6-(cyclopropylamino)-9H-purin-9-yl]-5-(3-methyl-1,2,4-oxadiazol-5-yl)tetrahydrofuran-3,4-diol	Analogous method to route G	LC/ MS (System C) R_t 2.17 min. Mass Spectrum *m/z* 360 [MH^+].
42	(2R,3R,4S,5S)-2-[6-(2-fluoroanilino)-9H-purin-9-yl]-5-(3-methyl-1,2,4-oxadiazol-5-yl)tetrahydrofuran-3,4-diol	Analogous method to route G	LC/ MS (System C) R_t 2.71 min. Mass Spectrum *m/z* 414 [MH^+].
43	(2R,3R,4S,5S)-2-[6-(2,4-difluoroanilino)-9H-purin-9-yl]-5-(3-methyl-1,2,4-oxadiazol-5-yl)tetrahydrofuran-3,4-diol	Analogous method to route G	LC/ MS (System C) R_t 2.75 min. Mass Spectrum *m/z* 432 [MH^+].
44	(2S,3S,4R,5R)-2-[3-(tert-butyl)-1,2,4-oxadiazol-5-yl]-5-{6-[(cyclopropylmethyl)amino]-9H-purin-9-yl}tetrahydrofuran-3,4-diol	Analogous method to route N	LC/ MS (System C) R_t 2.77 min. Mass Spectrum *m/z* 416 [MH^+].
45	(2S,3S,4R,5R)-2-[3-(tert-butyl)-1,2,4-oxadiazol-5-yl]-5-[6-(isobutylamino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol	See Below (route N)	LC/ MS (System C) R_t 2.88 min. Mass Spectrum *m/z* 418 [MH^+].

Table 1. Examples			
Ex No	Name	Expt. Details (note 1)	Characterising data
46	2-[(9-{(2R,3R,4S,5S)-5-[3-(tert-butyl)-1,2,4-oxadiazol-5-yl]-3,4-dihydroxytetrahydrofuran-2-yl}-9H-purin-6-yl)amino]-N-methylethanesulfonamide	Analogous method to route N	LC/ MS (System C) R_t 2.54 min. Mass Spectrum *m/z* 483 [MH^+].
47	(2S,3S,4R,5R)-2-[3-(tert-butyl)-1,2,4-oxadiazol-5-yl]-5-{6-[(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)amino]-9H-purin-9-yl}tetrahydrofuran-3,4-diol	Analogous method to route N	LC/ MS (System C) R_t 2.51 min. Mass Spectrum *m/z* 494 [MH^+].
48	(2S,3S,4R,5R)-2-[3-(tert-butyl)-1,2,4-oxadiazol-5-yl]-5-[6-(2-chloro-4-fluoroanilino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol	Analogous method to route O	LC/ MS (System C) R_t 3.20 min. Mass Spectrum *m/z* 490 [MH^+].
49	(2S,3S,4R,5R)-2-[3-(tert-butyl)-1,2,4-oxadiazol-5-yl]-5-[6-(2,4-difluoroanilino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol	See below (route O)	LC/ MS (System C) R_t 3.03 min. Mass Spectrum *m/z* 474 [MH^+].
50	(2S,3S,4R,5R)-2-[3-(tert-butyl)-1,2,4-oxadiazol-5-yl]-5-[6-(3,4-difluoroanilino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol	Analogous method to route O	LC/ MS (System C) R_t 3.32 min. Mass Spectrum *m/z* 474 [MH^+].

Table 1. Examples			
Ex No	Name	Expt. Details (note 1)	Characterising data
51	(2R,3R,4S,5S)-2-[6-(cyclopropylamino)-9H-purin-9-yl]-5-(3-isopropyl-1,2,4-oxadiazol-5-yl)tetrahydrofuran-3,4-diol	Analogous method to route N	LC/ MS (System C) R_t 2.39 min. Mass Spectrum *m/z* 388 [MH^+].
52	(2R,3R,4S,5S)-2-[6-(isobutylamino)-9H-purin-9-yl]-5-(3-isopropyl-1,2,4-oxadiazol-5-yl)tetrahydrofuran-3,4-diol	Analogous method to route N	LC/ MS (System C) R_t 2.74 min. Mass Spectrum *m/z* 404 [MH^+].
53	(2R,3R,4S,5S)-2-{6-[(cyclopropylmethyl)amino]-9H-purin-9-yl}-5-(3-isopropyl-1,2,4-oxadiazol-5-yl)tetrahydrofuran-3,4-diol	Analogous method to route N	LC/ MS (System C) R_t 2.65 min. Mass Spectrum *m/z* 402 [MH^+].
54	2-({9-[(2R,3R,4S,5S)-3,4-dihydroxy-5-(3-isopropyl-1,2,4-oxadiazol-5-yl)tetrahydrofuran-2-yl]-9H-purin-6-yl}amino)-N-methylethanesulfonamide	Analogous method to route N	LC/ MS (System C) R_t 2.58 min. Mass Spectrum *m/z* 469 [MH^+].
55	(2R,3R,4S,5S)-2-[6-(2,4-difluoroanilino)-9H-purin-9-yl]-5-(3-isopropyl-1,2,4-oxadiazol-5-yl)tetrahydrofuran-3,4-diol	Analogous method to route O	LC/ MS (System C) R_t 2.96 min. Mass Spectrum *m/z* 460 [MH^+].
56	(2R,3R,4S,5S)-2-[6-(3,4-difluoroanilino)-9H-purin-9-yl]-5-(3-isopropyl-1,2,4-oxadiazol-5-yl)tetrahydrofuran-3,4-diol	Analogous method to route O	LC/ MS (System C) R_t 3.20 min. Mass Spectrum *m/z* 460 [MH^+].

Table 1. Examples			
Ex No	Name	Expt. Details (note 1)	Characterising data
57	(2R,3R,4S,5S)-2-[6-(4-fluoro-2-methylanilino)-9H-purin-9-yl]-5-(3-isopropyl-1,2,4-oxadiazol-5-yl)tetrahydrofuran-3,4-diol	Analogous method to route O	LC/ MS (System C) R_t 3.05 min. Mass Spectrum *m/z* 456 [MH^+].
58	(2S,3S,4R,5R)-2-[3-(dimethylamino)-1,2,4-oxadiazol-5-yl]-5-[6-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol	Analogous method to route G	TLC SiO_2 (Cl_2CH_2:EtOH:880NH_3 95:5:0.5) R_f = 0.2 Microanalysis Found C, 49.75; H, 5.90; N, 25.2. $C_{18}H_{24}N_8O_5$ requires C, 49.5; H, 5.65; N, 25.6
59	(2R,3R,4S,5S)-2-{6-[rel-(1S,2R,4R)-bicyclo[2.2.1]hept-2-ylamino]-9H-purin-9-yl}-5-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)tetrahydrofuran-3,4-diol	Analogous method to route G	LC/MS (System B) R_t 2.81min. Mass Spectrum *m/z* 440 [MH^+]
60	ethyl 4-({9-[(2R,3R,4S,5S)-5-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-3,4-dihydroxytetrahydrofuran-2-yl]-9H-purin-6-yl}amino)piperidine-1-carboxylate	Analogous method to route G	LC/MS (System B) R_t 2.57min. Mass Spectrum *m/z* 501 [MH^+]
61	(2S,3S,4R,5R)-2-[3-(tert-butyl)-1,2,4-oxadiazol-5-yl]-5-[6-(isopropylamino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol	Analogous method to route G	LC/MS (System B) R_t 2.69min. Mass Spectrum *m/z* 404 [MH^+]

Table 1. Examples			
Ex No	Name	Expt. Details (note 1)	Characterising data
62	(2R,3R,4S,5S)-2-[6-(4-chloro-2-fluoroanilino)-9H-purin-9-yl]-5-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)tetrahydrofuran-3,4-diol	Analogous method to route G	LC/MS (System B) R_t 3.05min. Mass Spectrum *m/z* 474 [MH^+]
63	ethyl 4-({9-[(2R,3R,4S,5S)-3,4-dihydroxy-5-(3-isopropyl-1,2,4-oxadiazol-5-yl)tetrahydrofuran-2-yl]-9H-purin-6-yl}amino)piperidine-1-carboxylate	Analogous method to route G	LC/MS (System B) R_t 2.73min. Mass Spectrum *m/z* 503 [MH^+]
64	(2R,3R,4S,5S)-2-{6-[rel-(1S,2R,4R)-bicyclo[2.2.1]hept-2-ylamino]-9H-purin-9-yl}-5-(3-isopropyl-1,2,4-oxadiazol-5-yl)tetrahydrofuran-3,4-diol	Analogous method to route G	LC/MS (System A) R_t 4.27min. Mass Spectrum *m/z* 442 [MH^+]
65	2-({9-[(2R,3R,4S,5S)-5-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-3,4-dihydroxytetrahydrofuran-2-yl]-9H-purin-6-yl}amino)-N-methylethanesulfonamide	Analogous method to route G	LC/MS (System B) R_t 2.33min. Mass Spectrum *m/z* 467 [MH^+]
66	(2R,3R,4S,5S)-2-[2-Chloro-6-(1-ethyl-propylamino)-purin-9-yl]-5-(3-propyl-isoxazol-5-yl)-tetrahydro-furan-3,4-diol formate	Analogous method to route L	LC/MS (System A) R_t 4.68min. Mass Spectrum *m/z* 451 [MH^+]

Table 1. Examples			
Ex No	Name	Expt. Details (note 1)	Characterising data
67	(2R,3S,4R,5R)-2-[5-(tert-butyl)-4H-1,2,4-triazol-3-yl]-5-[6-(4-chloro-2-fluoroanilino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol	Analogous method to route F	LC/MS (System C) R_t 3.01min. Mass Spectrum *m/z* 489 [MH^+]
68	(2R,3R,4S,5R)-2-[6-(2-chloro-4-fluoroanilino)-9H-purin-9-yl]-5-(5-isopropyl-4H-1,2,4-triazol-3-yl)tetrahydrofuran-3,4-diol	Analogous method to route F	LC/MS (System C) R_t 2.89min. Mass Spectrum *m/z* 475 [MH^+]
69	2-({9-[(2R,3R,4S,5S)-3,4-dihydroxy-5-(3-methyl-1,2,4-oxadiazol-5-yl)tetrahydrofuran-2-yl]-9H-purin-6-yl}amino)-N-methylethanesulfonamide	Analagous method to route G	Analysis: $C_{15}H_{20}N_8O_6S$ Found % C:40.93, H: 4.72 N: 24.89 Required % C:40.9,H:4.63,N:25.24 *M/Z* [M+H] 441
70	(2R,3R,4S,5S)-2-{6-[(trans-4-hydroxycyclohexyl)amino]-9H-purin-9-yl}-5-(5-methyl-1,3-oxazol-2-yl)tetrahydrofuran-3,4-diol	Analagous method to route D	M/Z [M+H] 417
71	(2S,3S,4R,5R)-2-(3-methyl-1,2,4-oxadiazol-5-yl)-5-(6-{[(1R)-1-methyl-2-phenylethyl]amino}-9H-purin-9-yl)tetrahydrofuran-3,4-diol	Analagous method to route G	Analysis: C21H23N7O4 Found % C:56.41, H: 5.32 N: 21.78 Required % C: 56.49, H:5.42, N:21.96

Table 1. Examples			
Ex No	Name	Expt. Details (note 1)	Characterising data
72	(2S,3S,4R,5R)-2-(5-ethyl-1,3-oxazol-2-yl)-5-{6-[(trans-4-hydroxycyclohexyl)amino]-9H-purin-9-yl}tetrahydrofuran-3,4-diol	Analagous method to route D	Analysis: C20H26N6O5 Found % C:54.5, H: 6.0 N: 18.8 Required % C:55.8,H:6.1,N:19.5 M/Z [M+H] 432
73	(2S,3S,4R,5R)-2-(5-ethyl-1,3-oxazol-2-yl)-5-[6-(3-fluoro-4-hydroxyanilino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol	Analagous method to route D	Analysis: C20H19FN6O5 Found % C:53.6, H: 4.65 N: 18.1 Required % C:53.2,H:4.5,N:18.6 M/Z [M+H] 443
74	(2R,3R,4S,5S)-2-[6-(3-fluoroanilino)-9H-purin-9-yl]-5-(5-methyl-1,3-oxazol-2-yl)tetrahydrofuran-3,4-diol	Analagous method to route D	M/Z [M+H] 413
75	(2S,3S,4R,5R)-2-(5-ethyl-1,3-oxazol-2-yl)-5-(6-{[(1S,2R)-2-fluorocyclopentyl]amino}-9H-purin-9-yl)tetrahydrofuran-3,4-diol	Analagous method to route D	M/Z [M+H] 419
76	(2R,3R,4S,5S)-2-[6-(4-fluoroanilino)-9H-purin-9-yl]-5-(5-methyl-1,3-oxazol-2-yl)tetrahydrofuran-3,4-diol	Analogous to route D. See below (route P) for synthesis of intermediate.	Rf = 0.18 (Dichloromethane: ethanol:880ammonia 100:10:1) M/Z [M+H] 413
77	(2S,3S,4R,5R)-2-[3-(tert-butyl)-1,2,4-oxadiazol-5-yl]-5-[6-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol	Analogous method to route G	LC/MS (System A) Rt2.53 min.Mass Spectrum m/z 446 [MH+].

Table 1. Examples			
Ex No	Name	Expt. Details (note 1)	Characterising data
78	(2R,3R,4S,5S)-2-{6-[rel-(1S,2R,4R)-bicyclo[2.2.1]hept-2-ylamino]-9H-purin-9-yl}-5-[3-(tert-butyl)-1,2,4-oxadiazol-5-yl]tetrahydrofuran-3,4-diol	Analogous method to route G	LC/MS (System A) Rt 3.03 min.Mass Spectrum m/z 456 [MH+].
79	ethyl 4-[(9-{(2R,3R,4S,5S)-5-[3-(tert-butyl)-1,2,4-oxadiazol-5-yl]-3,4-dihydroxytetrahydrofuran-2-yl}-9H-purin-6-yl)amino]piperidine-1-carboxylate	Analogous method to route G	LC/MS (System A) Rt 2.77 min.Mass Spectrum m/z 4517 [MH+].
80	2-[(9-{(2R,3R,4S,5S)-5-[3-(tert-butyl)isoxazol-5-yl]-3,4-dihydroxytetrahydrofuran-2-yl}-9H-purin-6-yl)amino]-N-methylethanesulfonamide	Analogous method to route I	LC/MS (System B) Rt 3.76 min.Mass Spectrum m/z 482 [MH+].
81	(2S,3S,4R,5R)-2-[3-(tert-butyl)isoxazol-5-yl]-5-(6-{[(1S,2S)-2-fluorocyclopentyl]amino}-9H-purin-9-yl)tetrahydrofuran-3,4-diol	Analogous method to route I	LC/MS (System B) Rt 4.20 min.Mass Spectrum m/z 447 [MH+].
82	ethyl 4-[(9-{(2R,3R,4S,5S)-5-[3-(tert-butyl)isoxazol-5-yl]-3,4-dihydroxytetrahydrofuran-2-yl}-9H-purin-6-yl)amino]piperidine-1-carboxylate	Analogous method to route I	LC/MS (System B) Rt 4.06 min.Mass Spectrum m/z 516 [MH+].

Table 1. Examples			
Ex No	Name	Expt. Details (note 1)	Characterising data
83	(2S,3S,4R,5R)-2-[3-(tert-butyl)isoxazol-5-yl]-5-[6-(cyclopentylamino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol	Analogous method to route I	LC/MS (System B) Rt 4.18 min. Mass Spectrum m/z 429 [MH+].
84	2-({9-[(2R,3R,4S,5S)-5-(5-ethyl-1,3-oxazol-2-yl)-3,4-dihydroxytetrahydrofuran-2-yl]-9H-purin-6-yl}amino)-N,N-dimethylethanesulfonamide	See below (route Q).	Mass Spectrum *m/z[MH]+ = 468*
85	2-({9-[(2R,3R,4S,5S)-5-(5-ethyl-1,3-oxazol-2-yl)-3,4-dihydroxytetrahydrofuran-2-yl]-9H-purin-6-yl}amino)-N-methylethanesulfonamide	Analagous method to route Q.	Mass Spectrum *m/z[MH]+ = 454*
86	ethyl 4-({9-[(2R,3R,4S,5S)-5-(5-ethyl-1,3-oxazol-2-yl)-3,4-dihydroxytetrahydrofuran-2-yl]-9H-purin-6-yl}amino)piperidine-1-carboxylate	Analagous to route Q.	Mass Spectrum *m/z[MH]+ = 488*
87	(2R,3R,4S,5S)-2-{6-[(2,3-dihydroxypropyl)amino]-9H-purin-9-yl}-5-(5-ethyl-1,3-oxazol-2-yl)tetrahydrofuran-3,4-diol	Analagous to route Q.	Mass Spectrum *m/z[MH]+ = 407*
88	(2R,3R,4S,5S)-2-[6-(2,4-difluoroanilino)-9H-purin-9-yl]-5-(5-ethyl-1,3-oxazol-2-yl)tetrahydrofuran-3,4-diol	Analagous to route Q.	Mass Spectrum *m/z[MH]+ = 445*

Table 1. Examples			
Ex No	Name	Expt. Details (note 1)	Characterising data
89	(2S,3S,4R,5R)-2-(5-ethyl-1,3-oxazol-2-yl)-5-(6-{[(1S,2S)-2-hydroxycyclopentyl]amino}-9H-purin-9-yl)tetrahydrofuran-3,4-diol	Analagous to route Q.	Mass Spectrum *m/z[MH]+ = 417*
90	(2S,3S,4R,5R)-2-(5-ethyl-1,3-oxazol-2-yl)-5-{6-[(3R)-tetrahydrofuran-3-ylamino]-9H-purin-9-yl}tetrahydrofuran-3,4-diol	Analagous to route Q.	Mass Spectrum *m/z[MH]+ = 403*
91	(2R,3R,4S,5S)-2-(6-{[(1R)-2-methoxy-1-methylethyl]amino}-9H-purin-9-yl)-5-(5-methyl-1,3,4-oxadiazol-2-yl)tetrahydrofuran-3,4-diol	Analagous method to route C	Microanalysis Found: C,46.7; H,5.3; N,23.6. $C_{16}H_{21}N_7O_5$ requires: C,46.9; H, 5.7; N,23.95.
92	(2R,3R,4S,5S)-2-[6-(cyclopentylamino)-9H-purin-9-yl]-5-(3-methyl-1,2,4-oxadiazol-5-yl)tetrahydrofuran-3,4-diol	See below (route R).	TLC SiO_2 (ethyl acetate:methanol 19:1) Rf = 0.30 NMR (DMSO) 8.43 (1H,s,CH); 8.20 (1H,br.s,CH); 7.79 (1H,br.d,NH); 6.45 (2H, v.br.s ,2x OH); 6.16 (1H,d,CH); 5.24 (1H,d,CH); 4.89 (1H,t,CH); 4.73 (1H,t,CH); 4.58 (1H,br.m,CH); 2.42 (3H,s,Me); 2.10-1.50 (8H,m,4xCH_2)

Table 1. Examples			
Ex No	Name	Expt. Details (note 1)	Characterising data
93	(2R,3R,4S,5S)-2-(6-{[(1R,2R)-2-hydroxycyclopentyl]amino}-9H-purin-9-yl)-5-(5-phenyl-1,3,4-oxadiazol-2-yl)tetrahydrofuran-3,4-diol	Analagous method to route A	TLC SiO_2 (CH_2Cl_2:MeOH: 880NH_3 92:8:0.3) Rf = 0.14 Microanalysis Found: C,55.7; H,5.1; N,20.5. $C_{22}H_{23}N_7O_5$ requires: C,55.7; H, 5.1; N,20.7
94	(2R,3R,4S,5S)-2-{6-[rel-(1S,5S,6R)-bicyclo[3.2.0]hept-6-ylamino]-9H-purin-9-yl}-5-(3-methyl-1,2,4-oxadiazol-5-yl)tetrahydrofuran-3,4-diol	Analagous method to route G	Microanalysis Found: C,54.2; H,5.7; N,22.65. $C_{19}H_{23}N_7O_4$. 0.5MeOH requires: C,54.5; H, 5.9; N,22.8.
95	(2R,3R,4S,5S)-2-{6-[rel-(1S,2S,4R)-bicyclo[2.2.1]hept-2-ylamino]-9H-purin-9-yl}-5-(3-methyl-1,2,4-oxadiazol-5-yl)tetrahydrofuran-3,4-diol	Analagous method to route G	Microanalysis Found: C,54.4; H,5.7; N,23.1. $C_{19}H_{23}N_7O_4$. 0.4H_2O requires: C,54.25; H, 5.7; N,23.3.
96	(2R,3R,4S,5S)-2-{6-[rel-(1S,2R,4R)-bicyclo[2.2.1]hept-2-ylamino]-9H-purin-9-yl}-5-[5-(tert-butyl)-1,3,4-oxadiazol-2-yl]tetrahydrofuran-3,4-diol	Analagous method to route A	LC/MS (System B) R_t = 3.18min Mass Spectrum *m/z* 544 [MH^+]
97	(2R,3R,4S,5S)-2-{6-[rel-(1S,2R,4R)-bicyclo[2.2.1]hept-2-ylamino]-9H-purin-9-yl}-5-(5-isopropyl-1,3,4-oxadiazol-2-yl)tetrahydrofuran-3,4-diol	Analagous method to route A	LC/MS (System B) R_t = 2.66min Mass Spectrum *m/z* 442 [MH^+]

Table 1. Examples			
Ex No	Name	Expt. Details (note 1)	Characterising data
98	ethyl 4-({9-[(2R,3R,4S,5S)-3,4-dihydroxy-5-(5-isopropyl-1,3,4-oxadiazol-2-yl)tetrahydrofuran-2-yl]-9H-purin-6-yl}amino)piperidine-1-carboxylate	Analagous method to route A	LC/MS (System B) R_t = 2.47min Mass Spectrum *m/z* 503 [MH^+]
99	2-[(9-{(2R,3R,4S,5S)-5-[5-(tert-butyl)-1,3,4-oxadiazol-2-yl]-3,4-dihydroxytetrahydrofuran-2-yl}-9H-purin-6-yl)amino]-N-methylethanesulfonamide	Analagous method to route A	LC/MS (System B) R_t = 2.32min Mass Spectrum *m/z* 483 [MH^+]
100	(2S,3S,4R,5R)-2-[5-(tert-butyl)-1,3,4-oxadiazol-2-yl]-5-(6-{[(1R,2R)-2-fluorocyclopentyl]amino}-9H-purin-9-yl)tetrahydrofuran-3,4-diol	Analagous method to route A	LC/MS (System B) R_t = 2.63min Mass Spectrum *m/z* 448 [MH^+]
101	(2S,3S,4R,5R)-2-[3-(tert-butyl)-1,2,4-oxadiazol-5-yl]-5-[6-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol	Analagous to route G	LC/MS (System B) R_t = 2.53min Mass Spectrum *m/z* 446 [MH^+]
102	(2R,3R,4S,5S)-2-{6-[rel-(1S,2R,4R)-bicyclo[2.2.1]hept-2-ylamino]-9H-purin-9-yl}-5-[3-(tert-butyl)-1,2,4-oxadiazol-5-yl]tetrahydrofuran-3,4-diol	Analagous to route G	LC/MS (System B) R_t = 3.03min Mass Spectrum *m/z* 456 [MH^+]

Table 1. Examples			
Ex No	Name	Expt. Details (note 1)	Characterising data
103	ethyl 4-[(9-{(2R,3R,4S,5S)-5-[3-(tert-butyl)-1,2,4-oxadiazol-5-yl]-3,4-dihydroxytetrahydrofuran-2-yl}-9H-purin-6-yl)amino]piperidine-1-carboxylate	Analagous to route G	LC/MS (System B) R_t = 2.77min Mass Spectrum *m/z* 517 [MH^+]
104	2-[(9-{(2R,3R,4S,5S)-5-[3-(tert-butyl)isoxazol-5-yl]-3,4-dihydroxytetrahydrofuran-2-yl}-9H-purin-6-yl)amino]-N-methylethanesulfonamide	Analagous to route I	LC/MS (System A) R_t = 3.76min Mass Spectrum *m/z* 482 [MH^+]
105	(2S,3S,4R,5R)-2-[3-(tert-butyl)isoxazol-5-yl]-5-(6-{[(1S,2S)-2-fluorocyclopentyl]amino}-9H-purin-9-yl)tetrahydrofuran-3,4-diol	Analagous to route I	LC/MS (System A) R_t = 4.20min Mass Spectrum *m/z* 447 [MH^+]
106	ethyl 4-[(9-{(2R,3R,4S,5S)-5-[3-(tert-butyl)isoxazol-5-yl]-3,4-dihydroxytetrahydrofuran-2-yl}-9H-purin-6-yl)amino]piperidine-1-carboxylate	Analagous to route I	LC/MS (System A) R_t = 4.06min Mass Spectrum *m/z* 516 [MH^+]
107	(2S,3S,4R,5R)-2-[3-(tert-butyl)isoxazol-5-yl]-5-[6-(cyclopentylamino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol	Analagous to route I	LC/MS (System A) R_t = 4.18min Mass Spectrum *m/z* 429 [MH^+]

Table 1. Examples			
Ex No	Name	Expt. Details (note 1)	Characterising data
108	(2S,3S,4R,5R)-2-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)-5-[6-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol	Analagous to route A	LC/MS (System D) R_t = 2.28min Mass Spectrum *m/z* 430 [MH^+]
109	(2S,3S,4R,5R)-2-(5-cyclopentyl-1,3,4-oxadiazol-2-yl)-5-(6-{[(1S,2S)-2-hydroxycyclopentyl]amino}-9H-purin-9-yl)tetrahydrofuran-3,4-diol	Analagous to route A	LC/MS (System D) R_t = 2.59min Mass Spectrum *m/z* 458 [MH^+]
110	ethyl 4-({9-[(2R,3R,4S,5S)-5-(5-cyclopentyl-1,3,4-oxadiazol-2-yl)-3,4-dihydroxytetrahydrofuran-2-yl]-9H-purin-6-yl}amino)piperidine-1-carboxylate	Analagous to route A	LC/MS (System D) R_t = 2.82min Mass Spectrum *m/z* 529 [MH^+]
111	(2S,3S,4R,5R)-2-(5-cyclopentyl-1,3,4-oxadiazol-2-yl)-5-(6-{[(1R,2R)-2-fluorocyclopentyl]amino}-9H-purin-9-yl)tetrahydrofuran-3,4-diol	Analagous to route A	LC/MS (System D) R_t = 2.93min Mass Spectrum *m/z* 460 [MH^+]
112	(2R,3R,4S,5S)-2-[6-(4-chloro-2-fluoroanilino)-9H-purin-9-yl]-5-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)tetrahydrofuran-3,4-diol	Analagous to route A	LC/MS (System B) R_t = 2.84min Mass Spectrum *m/z* 474 [MH^+]

Table 1: Examples			
Ex No	Name	Expt. Details (note 1)	Characterising data
113	(2R,3R,4S,5S)-2-[6-(4-chloro-2-fluoroanilino)-9H-purin-9-yl]-5-(5-cyclopentyl-1,3,4-oxadiazol-2-yl)tetrahydrofuran-3,4-diol	Analagous to route A	LC/MS (System B) R_t = 3.05min Mass Spectrum *m/z* 502 [MH^+]
114	(2S,3S,4R,5R)-2-[5-(tert-butyl)-1,3,4-oxadiazol-2-yl]-5-[6-(2-fluoroanilino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol	Analagous to route A	LC/MS (System D) R_t = 2.88min Mass Spectrum *m/z* 456 [MH^+]
115	(2S,3S,4R,5R)-2-[5-(tert-butyl)-1,3,4-oxadiazol-2-yl]-5-[6-(2,3-difluoroanilino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol	Analagous to route A	LC/MS (System D) R_t = 2.96min Mass Spectrum *m/z* 474 [MH^+]
116	(2S,3S,4R,5R)-2-[5-(tert-butyl)-1,3,4-oxadiazol-2-yl]-5-[6-(2-chloro-4-fluoroanilino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol	Analagous to route A	LC/MS (System D) R_t = 3.05min Mass Spectrum *m/z* 490 [MH^+]
117	(2S,3S,4R,5R)-2-[5-(tert-butyl)-1,3,4-oxadiazol-2-yl]-5-[6-(4-fluoro-2-methylanilino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol	Analagous to route A	LC/MS (System D) R_t = 2.86min Mass Spectrum *m/z* 470 [MH^+]
118	(2R,3R,4S,5R)-2-{2-chloro-6-[(1-ethylpropyl)amino]-9H-purin-9-yl}-5-(5-ethylisoxazol-3-yl)tetrahydrofuran-3,4-diol formate	See below (route S).	LC/MS (System C) R_t = 3.41min Mass Spectrum m/z 437 [MH^+]

Table 1. Examples			
Ex No	Name	Expt. Details (note 1)	Characterising data
119	(2S,3S,4R,5R)-2-[3-(tert-butyl)isoxazol-5-yl]-5-{6-[(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)amino]-9H-purin-9-yl}tetrahydrofuran-3,4-diol	Analagous to route I (last 2 steps reverse order)	LC/MS (System C) R_t = 2.61min Mass Spectrum *m/z* 493 [MH^+]
120	(2S,3S,4R,5R)-2-[3-(tert-butyl)isoxazol-5-yl]-5-[6-(2-chloro-4-fluoroanilino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol	Analagous to route I (last 2 steps reverse order)	LC/MS (System C) R_t = 3.29min Mass Spectrum *m/z* 489/491 [MH^+]
121	(2S,3S,4R,5R)-2-[3-(tert-butyl)isoxazol-5-yl]-5-[6-(4-fluoro-2-methylanilino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol	Analagous to route I (last 2 steps reverse order)	LC/MS (System C) R_t = 3.09min Mass Spectrum *m/z* 469 [MH^+]
122	(2S,3S,4R,5R)-2-[3-(tert-butyl)isoxazol-5-yl]-5-[6-(2-chloroanilino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol	Analagous to route I (last 2 steps reverse order)	LC/MS (System C) R_t = 3.25min Mass Spectrum *m/z* 471/473 [MH^+]
123	2-[(9-{(2R,3R,4S,5S)-5-[5-(tert-butyl)-1,3,4-oxadiazol-2-yl]-3,4-dihydroxytetrahydrofuran-2-yl}-9H-purin-6-yl)amino]-N-ethylethanesulfonamide	Analogous to route T	LC/ MS (System C) R_t 2.52 min. Mass Spectrum *m/z* 497 [MH^+].
124	(2S,3S,4R,5R)-2-[5-(tert-butyl)-1,3,4-oxadiazol-2-yl]-5-(6-{[2-(ethylsulfonyl)ethyl]amino}-9H-purin-9-	Analogous to route A	LC/ MS (System C) R_t 2.45 min. Mass Spectrum *m/z* 482 [MH^+].

Table 1. Examples			
Ex No	Name	Expt. Details (note 1)	Characterising data
	yl)tetrahydrofuran-3,4-diol		
125	(2S,3S,4R,5R)-2-[5-(tert-butyl)-1,3,4-oxadiazol-2-yl]-5-(6-{[2-(butylsulfonyl)ethyl]amino}-9H-purin-9-yl)tetrahydrofuran-3,4-diol	Analogous to route A	LC/ MS (System C) R_t 2.6 min. Mass Spectrum *m/z* 510 [MH^+].
126	2-[(9-{(2R,3R,4S,5S)-5-[5-(tert-butyl)-1,3,4-oxadiazol-2-yl]-3,4-dihydroxytetrahydrofuran-2-yl}-9H-purin-6-yl)amino]-N-(3-methylphenyl)ethanesulfonamide	Analogous to route A	LC/ MS (System C) R_t 2.79 min. Mass Spectrum *m/z* 559 [MH^+].
127	2-({9-[(2R,3R,4S,5S)-3,4-dihydroxy-5-(5-methyl-1,3-oxazol-2-yl)tetrahydrofuran-2-yl]-9H-purin-6-yl}amino)-N-methylethanesulfonamide	Route V	Mass Spectrum *m/z* 440 [MH^+]. TLC SiO_2 (dichloromethane:ethanol:ammonia 50:8:1) R_f 0.21.
128	2-[(9-{(2R,3R,4S,5S)-5-[5-(tert-butyl)-1,3,4-oxadiazol-2-yl]-3,4-dihydroxytetrahydrofuran-2-yl}-9H-purin-6-yl)amino]-N-phenylethanesulfonamide	Analogous to route A	LC/ MS (System C) R_t 2.7 min. Mass Spectrum *m/z* 545 [MH^+].

Table 1. Examples			
Ex No	Name	Expt. Details (note 1)	Characterising data
129	(2R,3R,4S,5S)-2-[6-(cyclopentylamino)-9H-purin-9-yl]-5-[3-(methoxymethyl)-1,2,4-oxadiazol-5-yl]tetrahydrofuran-3,4-diol	Analogous to route G	Analysis: Found (%): C 49.5; H 5.4; N 21.9. Required for $C_{18}H_{23}N_7O_5.1.2\ H_2O$ C 49.3; H 5.8; N 22.3.
130	(2R,3R,4S,5R)-2-[6-(cyclopentylamino)-9H-purin-9-yl]-5-(1,5-dimethyl-1H-1,2,4-triazol-3-yl)tetrahydrofuran-3,4-diol trifluoroacetate	Route X	Analysis: Found (%): C 44.4; H 4.8; N 20.4. Required for $C_{18}H_{24}N_8O_3.CF_3CO_2H.1.5\ H_2O$ C 44.4; H 5.2; N 20.7.
131	(2S,3S,4R,5R)-2-(5-ethyl-1,3,4-oxadiazol-2-yl)-5-[6-(isopropylamino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol	From Intermediate 17, analagous to route C	Analysis: Found (%): C 50.0; H 5.7; N 24.7. $C_{16}H_{21}N_7O_4.0.1\ CH_2Cl_2$. 0.1 H_2O requires C 50.1; H 5.6; N 25.4. TLC SiO_2 (dichloromethane: methanol: ammonia 94:6:1) R_f 0.21.
132	(2R,3R,4S,5S)-2-(6-{[(1S,2S)-2-hydroxycyclopentyl]amino}-9H-purin-9-yl)-5-(5-methyl-1,3,4-oxadiazol-2-yl)tetrahydrofuran-3,4-diol	Analagous to route A	Analysis: Found (%): C 48.9; H 5.4; N 21.8. $C_{17}H_{21}N_7O_5$. 0.9 H_2O. 0.4EtOAc requires C 49.1; H 5.8; N 21.6. TLC SiO_2 (ethyl acetate:methanol 7:1) R_f 0.45.
133	(2S,3S,4R,5R)-2-[3-(methyl)-1,2,4-oxadiazol-5-yl]-5-[6-(2-chloro-4-fluoroanilino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol	Analagous to route G	LC/ MS (System C) R_t 2.91 min. Mass Spectrum *m/z* 448 [MH^+].

Table 1. Examples			
Ex No	Name	Expt. Details (note 1)	Characterising data
134	(2R,3R,4S,5S)-2-{2-chloro-6-[(1-ethylpropyl)amino]-9H-purin-9-yl}-5-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)tetrahydrofuran-3,4-diol formate (1:2)	Analagous to routes B and R	LC/ MS (System C) R_t 3.22 min. Mass Spectrum *m/z* 450 [MH^+].
135	(2S,3S,4R,5R)-2-(3-ethylisoxazol-5-yl)-5-[6-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol	Analagous to route L	LC/ MS (System C) R_t 2.46 min. Mass Spectrum *m/z* 417 [MH^+].
136	(2S,3S,4R,5R)-2-(3-ethylisoxazol-5-yl)-5-(6-{[(1S,2S)-2-hydroxycyclopentyl]amino}-9H-purin-9-yl)tetrahydrofuran-3,4-diol	Analagous to route L	LC/ MS (System C) R_t 2.51 min. Mass Spectrum *m/z* 417 [MH^+].
137	N-ethyl-2-({9-[(2R,3R,4S,5S)-5-(3-ethylisoxazol-5-yl)-3,4-dihydroxytetrahydrofuran-2-yl]-9H-purin-6-yl}amino)ethanesulfonamide	Analagous to route L	LC/ MS (System C) R_t 2.53 min. Mass Spectrum *m/z* 468 [MH^+].
138	ethyl 4-({9-[(2R,3R,4S,5S)-5-(3-ethylisoxazol-5-yl)-3,4-dihydroxytetrahydrofuran-2-yl]-9H-purin-6-yl}amino)piperidine-1-carboxylate	Analagous to route L	LC/ MS (System C) R_t 2.74 min. Mass Spectrum *m/z* 488 [MH^+].

Table 1. Examples			
Ex No	Name	Expt. Details (note 1)	Characterising data
139	(2R,3S,4R,5R)-2-[5-(tert-butyl)-4H-1,2,4-triazol-3-yl]-5-[6-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol	Analogous to route F	LC/ MS (System C) R_t 2.30 min. Mass Spectrum *m/z* 445 [MH^+].
140	(2R,3R,4S,5R)-2-[6-(4-chloro-2-fluoroanilino)-9H-purin-9-yl]-5-(4H-1,2,4-triazol-3-yl)tetrahydrofuran-3,4-diol	Analogous to route F	LC/ MS (System C) R_t 2.47 min. Mass Spectrum *m/z* 433 [MH^+].
141	(2R,3S,4R,5R)-2-(5-isopropyl-4H-1,2,4-triazol-3-yl)-5-[6-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol	Analogous to route F	LC/ MS (System C) R_t 2.21 min. Mass Spectrum *m/z* 431 [MH^+].
142	(2R,3R,4S,5S)-2-(6-amino-2-chloro-9H-purin-9-yl)-5-(5-methyl-1,3-oxazol-2-yl)tetrahydrofuran-3,4-diol	Analogous to route Q	Analysis: Found (%): C 43.73; H 3.32; N 23.04. $C_{13}H_{131}N_6O_4Cl.0.1\ CF_3CO_2H$). requires C 43.54; H 3.63; N 23.08. Mass Spectrum *m/z* 353 [MH^+].
143	(2R,3R,4S,5S)-2-[2-chloro-6-(2-chloro-4-fluoroanilino)-9H-purin-9-yl]-5-(5-methyl-1,3-oxazol-2-yl)tetrahydrofuran-3,4-diol	Analogous to route Q	LC/ MS (System C) R_t 3.19 min. Mass Spectrum *m/z* 482 [MH^+].

Table 1. Examples			
Ex No	Name	Expt. Details (note 1)	Characterising data
144	(2R,3R,4S,5S)-2-[6-(4-chloro-2-fluoroanilino)-9H-purin-9-yl]-5-(3-methylisoxazol-5-yl)tetrahydrofuran-3,4-diol	Route Wb	LC/ MS (System C) R_t 2.95 min. Mass Spectrum *m/z* 447 [MH^+].
145	(2R,3R,4S,5S)-2-[6-(4-chloro-2-fluoroanilino)-9H-purin-9-yl]-5-(3-propylisoxazol-5-yl)tetrahydrofuran-3,4-diol	Analogous to route Wb	LC/ MS (System C) R_t 3.23 min. Mass Spectrum *m/z* 475 [MH^+].
146	2-[(9-{(2R,3R,4S,5S)-5-[3-(tert-butyl)isoxazol-5-yl]-3,4-dihydroxytetrahydrofuran-2-yl}-9H-purin-6-yl)amino]-N-isopropylethanesulfonamide	Analogous to route I	LC/ MS (System C) R_t 32.75 min. Mass Spectrum *m/z* 510 [MH^+].
147	(2R,3R,4S,5S)-2-[2-chloro-6-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl]-5-(3-ethylisoxazol-5-yl)tetrahydrofuran-3,4-diol	Analogous to route L	LC/ MS (System C) R_t 2.83min. Mass Spectrum *m/z* 451/453 [MH^+].
148	ethyl 4-({2-chloro-9-[(2R,3R,4S,5S)-5-(3-ethylisoxazol-5-yl)-3,4-dihydroxytetrahydrofuran-2-yl]-9H-purin-6-yl}amino)piperidine-1-carboxylate	Analogous to route L	LC/ MS (System C) R_t 3.10min. Mass Spectrum *m/z* 522/524 [MH^+].

Table 1. Examples			
Ex No	Name	Expt. Details (note 1)	Characterising data
149	(2R,3R,4S,5S)-2-(2-chloro-6-{[(1S,2S)-2-hydroxycyclopentyl]amino}-9H-purin-9-yl)-5-(3-ethylisoxazol-5-yl)tetrahydrofuran-3,4-diol	Analogous to route L	LC/ MS (System C) R_t 2.81min. Mass Spectrum *m/z* 451/453 [MH^+].
150	(2R,3R,4S,5S)-2-(2-chloro-6-{[2-(ethylsulfonyl)ethyl]amino}-9H-purin-9-yl)-5-(3-ethylisoxazol-5-yl)tetrahydrofuran-3,4-diol	Analogous to route L	LC/ MS System C R_t 2.75min. Mass Spectrum *m/z* 487/489 [MH^+].
151	(2R,3R,4S,5S)-2-[2-chloro-6-(4-chloro-2-fluoroanilino)-9H-purin-9-yl]-5-(3-ethylisoxazol-5-yl)tetrahydrofuran-3,4-diol	Analogous to route L	LC/ MS (System C) R_t 3.33min. Mass Spectrum *m/z* 495/497 [MH^+].
152	(2R,3R,4S,5S)-2-[2-chloro-6-(2-chloro-4-fluoroanilino)-9H-purin-9-yl]-5-(3-ethylisoxazol-5-yl)tetrahydrofuran-3,4-diol	Analogous to route L	LC/ MS (System C) R_t 3.23min. Mass Spectrum *m/z* 495 [MH^+].
153	(2R,3R,4S,5S)-2-[2-chloro-6-(2-fluoroanilino)-9H-purin-9-yl]-5-(3-ethylisoxazol-5-yl)tetrahydrofuran-3,4-diol	Analogous to route L	LC/ MS (System C) R_t 3.08min. Mass Spectrum *m/z* 461/463 [MH^+].

Table 1. Examples			
Ex No	Name	Expt. Details (note 1)	Characterising data
154	(2R,3R,4S,5S)-2-[2-chloro-6-(2-chloroanilino)-9H-purin-9-yl]-5-(3-ethylisoxazol-5-yl)tetrahydrofuran-3,4-diol	Analogous to route L	LC/ MS (System C) R_t 3.22min. Mass Spectrum *m/z* 477 [MH^+].
155	(2R,3R,4S,5S)-2-(6-{[(1S,2S)-2-hydroxycyclopentyl]amino}-9H-purin-9-yl)-5-[3-(hydroxymethyl)isoxazol-5-yl]tetrahydrofuran-3,4-diol	Analogous to route V	LC/ MS (System C) R_t 2.25min Mass Spectrum *m/z* 419 [MH^+].
156	ethyl 4-[(9-{(2R,3R,4S,5S)-3,4-dihydroxy-5-[3-(hydroxymethyl)isoxazol-5-yl]tetrahydrofuran-2-yl}-9H-purin-6-yl)amino]piperidine-1-carboxylate	Analogous to route V	LC/ MS (System C) R_t 2.46min. Mass Spectrum *m/z* 490 [MH^+].
157	(2S,3S,4R,5R)-2-[3-(hydroxymethyl)isoxazol-5-yl]-5-[6-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol	Analogous to route V	LC/ MS (System C) R_t 2.20min. Mass Spectrum *m/z* 419 [MH^+].
158	(2R,3R,4S,5S)-2-[6-(4-chloro-2-fluoroanilino)-9H-purin-9-yl]-5-(3-ethylisoxazol-5-yl)tetrahydrofuran-3,4-diol	Analogous to route L	LC/ MS (System C) R_t 3.10 min. Mass Spectrum *m/z* 461 [MH^+].

Table 1. Examples			
Ex No	Name	Expt. Details (note 1)	Characterising data
159	(2R,3R,4S,5S)-2-[6-(2-chloro-4-fluoroanilino)-9H-purin-9-yl]-5-(3-ethylisoxazol-5-yl)tetrahydrofuran-3,4-diol	Analogous to route L	LC/ MS (System C) R_t 2.99min. Mass Spectrum *m/z* 461 [MH^+].
160	(2S,3S,4R,5R)-2-(3-ethylisoxazol-5-yl)-5-[6-(2-fluoroanilino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol	Analogous to route L	LC/ MS (System C) R_t 2.81min. Mass Spectrum *m/z* 427 [MH^+].
161	(2R,3R,4S,5S)-2-[6-(2-chloroanilino)-9H-purin-9-yl]-5-(3-ethylisoxazol-5-yl)tetrahydrofuran-3,4-diol	Analogous to route L	LC/ MS (System C) R_t 2.98min. Mass Spectrum *m/z* 443 [MH^+].
162	(2S,3S,4R,5R)-2-[5-(tert-butyl)-1,3,4-oxadiazol-2-yl]-5-[6-(piperidin-4-ylamino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol	Analogous to route Y	LC/ MS (System C) R_t 2.11min. Mass Spectrum *m/z* 445 [MH^+].
163	(2R,3R,4S,5R)-2-{2-chloro-6-[(1-ethylpropyl)amino]-9H-purin-9-yl}-5-(5-ethylisoxazol-3-yl)tetrahydrofuran-3,4-diol formate	Route S	LC/ MS (System C) R_t 3.41 min. Mass Spectrum *m/z* 437 [MH^+].

Table 1. Examples			
Ex No	**Name**	**Expt. Details (note 1)**	**Characterising data**
164	(2S,3S,4R,5R)-2-(3-bromoisoxazol-5-yl)-5-[6-(4-chloro-2-fluoroanilino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol	Route W	LC/ MS (System C) R_t 3.22min. Mass Spectrum *m/z* 511 [MH^+].
165	(2R,3R,4S,5S)-2-[6-(4-chloro-2-fluoroanilino)-9H-purin-9-yl]-5-[3-(3,5-difluorophenyl)isoxazol-5-yl]tetrahydrofuran-3,4-diol	Analagous to route W	LC/ MS (System C) R_t 3.55min. Mass Spectrum *m/z* 545 [MH^+].
166	(2S,3S,4R,5R)-2-[3-(tert-butyl)isoxazol-5-yl]-5-(6-{[1-(methylsulfonyl)piperidin-4-yl]amino}-9H-purin-9-yl)tetrahydrofuran-3,4-diol	Analogous to Route Y	LC/ MS (System C) R_t 2.69 min. Mass Spectrum *m/z* 522 [MH^+]
167	(2S,3S,4R,5R)-2-[3-(tert-butyl)isoxazol-5-yl]-5-(6-{[1-(propylsulfonyl)piperidin-4-yl]amino}-9H-purin-9-yl)tetrahydrofuran-3,4-diol	Analogous to Route Y	LC/ MS (System C) R_t 2.90 min. Mass Spectrum *m/z* 550 [MH^+]
168	(2S,3S,4R,5R)-2-[3-(tert-butyl)isoxazol-5-yl]-5-(6-{[1-(isopropylsulfonyl)piperidin-4-yl]amino}-9H-purin-9-yl)tetrahydrofuran-3,4-diol	Analogous to Route Y	LC/ MS (System C) R_t 2.87 min. Mass Spectrum *m/z* 550 [MH^+]

Table 1. Examples			
Ex No	Name	Expt. Details (note 1)	Characterising data
169	(2S,3S,4R,5R)-2-[3-(tert-butyl)isoxazol-5-yl]-5-(6-{[1-(ethylsulfonyl)piperidin-4-yl]amino}-9H-purin-9-yl)tetrahydrofuran-3,4-diol	Analogous to Route Y	LC/ MS (System C) R_t 2.77 min. Mass Spectrum *m/z* 536 [MH^+]
170	(2S,3S,4R,5R)-2-[3-(tert-butyl)isoxazol-5-yl]-5-[2-chloro-6-(4-chloro-2-fluoroanilino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol	Analogous to Route I	LC/ MS (System C) R_t 3.60 min. Mass Spectrum *m/z* 524 [MH^+]
171	(2S,3S,4R,5R)-2-[3-(tert-butyl)isoxazol-5-yl]-5-[2-chloro-6-(2-chloro-4-fluoroanilino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol	Analogous to Route I	LC/ MS (System C) R_t 3.50 min. Mass Spectrum m/z 524 [MH^+]
172	2-[(9-{(2R,3R,4S,5S)-5-[3-(tert-butyl)isoxazol-5-yl]-3,4-dihydroxytetrahydrofuran-2-yl}-2-chloro-9H-purin-6-yl)amino]-N-ethylethanesulfonamide	Analogous to Route I	LC/ MS (System C) R_t 2.94 min. Mass Spectrum *m/z* 530 [M^+]
173	2-[(9-{(2R,3R,4S,5S)-5-[3-(tert-butyl)isoxazol-5-yl]-3,4-dihydroxytetrahydrofuran-2-yl}-2-chloro-9H-purin-6-yl)amino]-N-isopropylethanesulfonamide	Analogous to Route I	LC/ MS (System C) R_t 3.04 min. Mass Spectrum *m/z* 544 [M^+]

Table 1. Examples			
Ex No	Name	Expt. Details (note 1)	Characterising data
174	(2S,3S,4R,5R)-2-[3-(tert-butyl)isoxazol-5-yl]-5-[2-chloro-6-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol	Analogous to Route I	LC/ MS (System C) R_t 2.96 min. Mass Spectrum *m/z* 479 [MH^+]
175	(2R,3R,4S,5S)-2-[6-(4-chloro-2-fluoroanilino)-9H-purin-9-yl]-5-(3-pyridin-3-ylisoxazol-5-yl)tetrahydrofuran-3,4-diol	Analogous to Route W	LC/ MS (System C) R_t 3.02 min. Mass Spectrum *m/z* 510 [MH^+]
176	(2R,3R,4S,5S)-2-[6-(4-chloro-2-fluoroanilino)-9H-purin-9-yl]-5-[3-(4-hydroxybutyl)isoxazol-5-yl]tetrahydrofuran-3,4-diol	Analogous to Route W	LC/ MS (System C) R_t 3.35 min. Mass Spectrum *m/z* 505 [MH^+]
177	2-[(9-{(2R,3R,4S,5S)-5-[3-(tert-butyl)isoxazol-5-yl]-3,4-dihydroxytetrahydrofuran-2-yl}-9H-purin-6-yl)amino]-N-ethylethanesulfonamide	Analogous to Route I	LC/ MS (System C) R_t 2.65 min. Mass Spectrum *m/z* 496 [MH^+]
178	(2R,3R,4S,5S)-2-[6-(cyclopentylamino)-9H-purin-9-yl]-5-[5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl]tetrahydrofuran-3,4-diol	Analogous to Route A	LC/ MS (System C) R_t 2.80 min. Mass Spectrum *m/z* 442 [MH^+]

Table 1. Examples			
Ex No	**Name**	**Expt. Details (note 1)**	**Characterising data**
179	(2R,3R,4S,5S)-2-(6-{[(1S,2S)-2-hydroxycyclopentyl]amino}-9H-purin-9-yl)-5-[5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl]tetrahydrofuran-3,4-diol	Analogous to Route A	LC/ MS (System C) R_t 2.48 min. Mass Spectrum *m/z* 458 [MH^+]
180	ethyl 4-[(9-{(2R,3R,4S,5S)-3,4-dihydroxy-5-[5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl]tetrahydrofuran-2-yl}-9H-purin-6-yl)amino]piperidine-1-carboxylate	Analogous to Route A	LC/ MS (System C) R_t 2.74 min. Mass Spectrum *m/z* 529 [MH^+]
181	2R,3R,4S,5S)-2-[6-(4-chloro-2-fluoroanilino)-9H-purin-9-yl]-5-(5-methyl-1,3,4-oxadiazol-2-yl)tetrahydrofuran-3,4-diol	Analogous to Route Cc	LC/ MS (System C) R_t 2.77 min. Mass Spectrum *m/z* 448 [MH^+]
182	(2R,3R,4S,5S)-2-[6-(4-chloro-2-fluoroanilino)-9H-purin-9-yl]-5-(3-cyclopropylisoxazol-5-yl)tetrahydrofuran-3,4-diol	Analogous to Route W	LC/ MS (System C) R_t 3.15 min. Mass Spectrum *m/z* 473 [MH^+]

Table 1. Examples			
Ex No	Name	Expt. Details (note 1)	Characterising data
183	(2S,3S,4R,5R)-2-[3-(tert-butyl)isoxazol-5-yl]-5-(6-[(1-butyrylpiperidin-4-yl)amino]-9H-purin-9-yl)tetrahydrofuran-3,4-diol	Analogous to Route Y	LC/ MS (System C) R_t 2.74 min. Mass Spectrum *m/z* 514 [MH^+]
184	isopropyl 4-[(9-{(2R,3R,4S,5S)-5-[3-(tert-butyl)isoxazol-5-yl]-3,4-dihydroxytetrahydrofuran-2-yl}-9H-purin-6-yl)amino]piperidine-1-carboxylate	Analogous to Route Y	LC/ MS (System C) R_t 3.10 min. Mass Spectrum *m/z* 530 [MH^+]
185	(2S,3S,4R,5R)-2-[3-(tert-butyl)isoxazol-5-yl]-5-(6-{[1-(2,2,2-trifluoroacetyl)piperidin-4-yl]amino}-9H-purin-9-yl)tetrahydrofuran-3,4-diol	Analogous to Route Y	LC/ MS (System C) R_t 3.05 min. Mass Spectrum *m/z* 540[MH^+]
186	methyl 4-[(9-{(2R,3R,4S,5S)-5-[3-(tert-butyl)isoxazol-5-yl]-3,4-dihydroxytetrahydrofuran-2-yl}-9H-purin-6-yl)amino]piperidine-1-carboxylate	Analogous to Route Y	LC/ MS (System C) R_t 2.73 min. Mass Spectrum *m/z* 502 [MH^+]

Table 1. Examples			
Ex No	Name	Expt. Details (note 1)	Characterising data
187	(2R,3R,4S,5S)-2-[6-(4-chloro-2-fluoroanilino)-9H-purin-9-yl]-5-[3-(hydroxymethyl)isoxazol-5-yl]tetrahydrofuran-3,4-diol	Analogous to Route V	LC/ MS (System C) R_t 2.67 min. Mass Spectrum *m/z* 463 [MH^+]
188	(2R,3R,4S,5S)-2-[6-(2-chloro-4-fluoroanilino)-9H-purin-9-yl]-5-[3-(hydroxymethyl)isoxazol-5-yl]tetrahydrofuran-3,4-diol	Analogous to Route V	LC/ MS (System C) R_t 2.56 min. Mass Spectrum *m/z* 463 [MH^+]
189	(2R,3R,4S,5S)-2-[6-(2-fluoroanilino)-9H-purin-9-yl]-5-[3-(hydroxymethyl)isoxazol-5-yl]tetrahydrofuran-3,4-diol	Analogous to Route V	LC/ MS (System C) R_t 2.40 min. Mass Spectrum *m/z* 429 [MH^+]
190	(2R,3R,4S,5S)-2-[6-(2-chloroanilino)-9H-purin-9-yl]-5-[3-(hydroxymethyl)isoxazol-5-yl]tetrahydrofuran-3,4-diol	Analogous to Route V	LC/ MS (System C) R_t 2.54 min. Mass Spectrum *m/z* 445 [MH^+]
191	(2R,3R,4S,5S)-2-(2-chloro-6-{[(1S,2S)-2-hydroxycyclopentyl]amino}-9H-purin-9-yl)-5-[3-(hydroxymethyl)isoxazol-5-yl]tetrahydrofuran-3,4-diol	Analogous to Route Bb	LC/ MS (System C) R_t 2.32 min. Mass Spectrum *m/z* 453/455 [MH^+]

Table 1. Examples			
Ex No	**Name**	**Expt. Details (note 1)**	**Characterising data**
192	(2R,3R,4S,5S)-2-[2-chloro-6-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl]-5-[3-(hydroxymethyl)isoxazol-5-yl]tetrahydrofuran-3,4-diol	Analogous to Route Bb	LC/ MS (System C) R_t 2.32 min. Mass Spectrum *m/z* 453/455 [MH^+]
193	2-[(2-chloro-9-{(2R,3R,4S,5S)-3,4-dihydroxy-5-[3-(hydroxymethyl)isoxazol-5-yl]tetrahydrofuran-2-yl}-9H-purin-6-yl)amino]-N-ethylethanesulfonamide	Analogous to Route Bb	LC/ MS (System C) R_t 2.32 min. Mass Spectrum *m/z* 504/506 [MH^+]
194	ethyl 4-[(2-chloro-9-{(2R,3R,4S,5S)-3,4-dihydroxy-5-[3-(hydroxymethyl)isoxazol-5-yl]tetrahydrofuran-2-yl}-9H-purin-6-yl)amino]piperidine-1-carboxylate	Analogous to Route Bb	LC/ MS (System C) R_t 2.60min. Mass Spectrum *m/z* 524 [MH^+]
195	(2R,3R,4S,5S)-2-[2-chloro-6-(4-chloro-2-fluoroanilino)-9H-purin-9-yl]-5-[3-(hydroxymethyl)isoxazol-5-yl]tetrahydrofuran-3,4-diol	Analogous to Route Bb	LC/ MS (System C) R_t 3.10 min. Mass Spectrum *m/z* 497 [MH^+]

Table 1. Examples			
Ex No	Name	Expt. Details (note 1)	Characterising data
196	(2R,3R,4S,5S)-2-[2-chloro-6-(2-chloro-4-fluoroanilino)-9H-purin-9-yl]-5-[3-(hydroxymethyl)isoxazol-5-yl]tetrahydrofuran-3,4-diol	Analogous to Route Bb	LC/ MS (System C) R_t 3.02 min. Mass Spectrum *m/z* 497/499 [MH^+]
197	(2R,3R,4S,5S)-2-[2-chloro-6-(2-fluoroanilino)-9H-purin-9-yl]-5-[3-(hydroxymethyl)isoxazol-5-yl]tetrahydrofuran-3,4-diol	Analogous to Route Bb	LC/ MS (System C) R_t 2.72 min. Mass Spectrum *m/z* 463 [MH^+]
198	(2S,3S,4R,5R)-2-(3-ethylisoxazol-5-yl)-5-[2-methoxy-6-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol	Analogous to Route L	LC/ MS (System C) R_t 2.57 min.. Mass Spectrum *m/z* 447 [MH^+]
199	ethyl 4-({9-[(2R,3R,4S,5S)-5-(3-ethylisoxazol-5-yl)-3,4-dihydroxytetrahydrofuran-2-yl]-2-methoxy-9H-purin-6-yl}amino)piperidine-1-carboxylate	Analogous to Route L	LC/ MS (System C) R_t 2.75 min. Mass Spectrum *m/z* 518 [MH^+]
200	(2S,3S,4R,5R)-2-(3-ethylisoxazol-5-yl)-5-(6-{[(1S,2S)-2-hydroxycyclopentyl]amino}-2-methoxy-9H-purin-9-yl)tetrahydrofuran-3,4-diol	Analogous to Route L	LC/ MS (System C) R_t 2.66 min. Mass Spectrum *m/z* 447 [MH^+]

Table 1. Examples			
Ex No	Name	Expt. Details (note 1)	Characterising data
201	(2S,3S,4R,5R)-2-(3-ethylisoxazol-5-yl)-5-(6-{[2-(ethylsulfonyl)ethyl]amino}-2-methoxy-9H-purin-9-yl)tetrahydrofuran-3,4-diol	Analogous to Route L	LC/ MS (System C) R_t 2.42 min. Mass Spectrum *m/z* 483 [MH^+]
202	(2R,3R,4S,5S)-2-[6-(2-chloro-4-fluoroanilino)-2-methoxy-9H-purin-9-yl]-5-(3-ethylisoxazol-5-yl)tetrahydrofuran-3,4-diol	Analogous to Route L	LC/ MS (System C) R_t 3.12 min. Mass Spectrum *m/z* 491 [MH^+]
203	(2S,3S,4R,5R)-2-(3-ethylisoxazol-5-yl)-5-[6-(2-fluoroanilino)-2-methoxy-9H-purin-9-yl]tetrahydrofuran-3,4-diol	Analogous to Route L	LC/ MS (System C) R_t 2.95 min. Mass Spectrum *m/z* 457 [MH^+]
204	(2R,3R,4S,5S)-2-[6-(4-chloro-2-fluoroanilino)-2-methoxy-9H-purin-9-yl]-5-(3-ethylisoxazol-5-yl)tetrahydrofuran-3,4-diol	Analogous to Route L	LC/ MS (System C) R_t 3.20 min. Mass Spectrum *m/z* 491 [MH^+]
205	(2S,3S,4R,5R)-2-[3-(tert-butyl)-1,2,4-oxadiazol-5-yl]-5-[6-(cyclopropylamino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol	Analogous to Route N	LC/ MS (System C) R_t 2.53 min. Mass Spectrum *m/z* 402 [MH^+]

Table 1. Examples			
Ex No	Name	Expt. Details (note 1)	Characterising data
206	(2S,3S,4R,5R)-2-[5-(tert-butyl)-1,3,4-oxadiazol-2-yl]-5-[2-chloro-6-(4-chloro-2-fluoroanilino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol	Analogous to route Cc	LC/ MS (System C) R_t 3.32 min. Mass Spectrum *m/z* 524 [MH^+]
207	(2R,3R,4S,5S)-2-[6-(4-chloro-2-fluoroanilino)-9H-purin-9-yl]-5-(5-isopropyl-1,3,4-oxadiazol-2-yl)tetrahydrofuran-3,4-diol	Analogous to Route Z	LC/ MS (System C) R_t 2.96 min. Mass Spectrum *m/z* 476 [MH^+]

Experimental details for route (A)

Intermediate 1

(3aS,4S,6R,6aR)-6-(6-Chloro-purin-9-yl)-2,2-dimethyl-tetrahydro-furo[3,4-d][1,3] dioxole-4-carboxylic acid N'-(2,2-dimethyl-propionyl)-hydrazide

(3aS,4S,6R,6aR)-6-(6-Chloro-purin-9-yl)-2,2-dimethyl-tetrahydro-furo[3,4-d][1,3] dioxole-4-carboxylic acid (2.5g) suspended in 1,2-dimethoxymethane (100ml) was treated with 2,2-dimethyl-propionic acid hydrazide (1.1g) and 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ), and the mixture heated under reflux for 16h. The mixture was poured into aqueous citric acid (250ml) and extracted with ethyl acetate; the organic layers were washed with citric acid and brine, dried ($MgSO_4$) and evaporated in vacuo to give the crude product. Purification by flash chromatography on silica gel (Biotage cartridge), eluting with ethyl acetate:cyclohexane 65:35, gave the title compound as a white solid (1.92g).

LC/MS (System B): R_t 2.49 min

Mass spectrum *m/z* 439 [MH^+].

Intermediate 2

9-[6S-(5-tert-Butyl-[1,3,4]oxadiazol-2-yl)-2,2-dimethyl-tetrahydro-(3aR,6aS)-furo[3,4-d][1,3]dioxol-4R-yl]-6-chloro-9H-purine

(3aS,4S,6R,6aR)-6-(6-Chloro-purin-9-yl)-2,2-dimethyl-tetrahydro-furo[3,4-d][1,3]dioxole-4-carboxylic acid N'-(2,2-dimethyl-propionyl)-hydrazide (1.5g) was dissolved in thionyl chloride (15ml) and the solution irradiated in a microwave oven at 150W power for 7 min. The excess thionyl chloride was evaporated in vacuo to give the crude product which was dissolved in dry acetonitrile (6ml) and heated under reflux for 3h. The solvent was evaporated and the residue purified by flash chromatography on silica gel, eluting with ethyl acetate:cyclohexane 35:65 – 40:60, to give the title compound as a white solid (0.645g).

LC/MS (System B): R_t 2.86min
Mass spectrum *m/z* 421 [MH^+].

Intermediate 3

(2S,3S,4R,5R)-2-(5-tert-Butyl-[1,3,4]oxadiazol-2-yl)-5-(6-chloro-purin-9-yl)-tetrahydro-furan-3,4-diol

9-[6S-(5-tert-Butyl-[1,3,4]oxadiazol-2-yl)-2,2-dimethyl-tetrahydro-(3aR,6aS)-furo[3,4-d][1,3]dioxol-4R-yl]-6-chloro-9H-purine (0.64g) was treated with 10:1 trifluoroacetic acid:water (9ml) at 0°C for 5h, and the mixture was allowed to stand in the refrigerator (2°) overnight. The mixture was evaporated in vacuo to low volume (ca. 1ml), poured into ice cold aqueous sodium bicarbonate, and extracted with ethyl acetate (3x50ml). The organic layers were washed with brine, dried ($MgSO_4$) and evaporated in vacuo to give the crude product (371mg).
LC/MS (System B) R_t 2.42 min
Mass spectrum *m/z* 381 [MH^+].

Example 3

(2S,3S,4R,5R)-2-(5-tert-Butyl-[1,3,4]oxadiazol-2-yl)-5-[6-(tetrahydro-pyran-4-ylamino)-purin-9-yl]-tetrahydro-furan-3,4-diol

(2S,3S,4R,5R)-2-(5-tert-Butyl-[1,3,4]oxadiazol-2-yl)-5-(6-chloro-purin-9-yl)-tetrahydro-furan-3,4-diol (41mg) was heated under reflux with 4-aminotetrahydropyran hydrochloride (59mg), diisopropylethylamine (0.11ml), and isopropanol (5ml) for 15h. The solvent was evaporated in vacuo and the residue purified by chromatography on silica gel, eluting with ethyl acetate:methanol 100:0 – 90:10, to give the title compound (37mg).

LC/MS (System B) R_t 2.31 min.
Mass Spectrum *m/z* 446 [MH^+].

Experimental details for route (B)

Intermediate 4
2-Chloro-N-(tetrahydro-pyran-4-yl)-adenosine

A mixture of acetic acid 4R-acetoxy-5R-acetoxymethyl-2R-(2,6-dichloro-purin-9-yl)-tetrahydro-furan-3R-yl ester (10g), diisopropylethylamine (5.7ml), and 4-amino tetrahydropyran hydrochloride (2.02g), in isopropanol (200ml) was heated at 50° for 4h. The cooled mixture was evaporated in vacuo, the residue re-dissolved in methanol (200ml) and ammonia gas bubbled through the solution for 2h. The mixture was stirred at 22°C overnight, and evaporated in vacuo to give a brown oily solid. Purification by flash chromatography on silica gel (Merck 9385), eluting with 75:8:1 DCM:EtOH:880NH_3 to 50:8:1 DCM:EtOH:880NH_3, gave the title compound as a pale brown oily solid (7.81g).
LC/MS (System B) Rt 2.24 min.
Mass spectrum *m/z* 3.86 [MH^+].

Intermediate 5
{6R-[2-Chloro-6-(tetrahydro-pyran-4-ylamino)-purin-9-yl]-2,2-dimethyl-tetrahydro-(3aR,6aR)-furo[3,4-d][1,3]dioxol-4R-yl}-methanol

A solution of 2-chloro-N-(tetrahydro-pyran-4-yl)-adenosine (7.81g) in acetone (500ml) was treated with 2,2-dimethoxypropane (14.7ml) and p-toluenesulphonic acid (3.8g) and the mixture was stirred at 22°C overnight. A white precipitate formed. The mixture was evaporated in vacuo, and the residue partitioned between ethyl acetate (700ml) and aqueous sodium bicarbonate solution (500ml). The organic layer was washed with aqueous sodium bicarbonate (2x250ml), dried (Na_2SO_4) and evaporated in vacuo to give a pale brown foam (7g). Purification by flash chromatography on silica gel (Merck 9385), eluting with ethyl acetate:cyclohexane 4:1, gave the title compound as a pale yellow foam (5.7g).
LC/MS (System B) Rt 2.68 min.
Mass spectrum *m/z* 426 [MH^+].

Intermediate 6

(3aS,4S,6R,6aR)-6-[2-Chloro-6-(tetrahydro-pyran-4-ylamino)-purin-9-yl]-2,2-dimethyl-tetrahydro-furo[3,4-d][1,3]dioxole-4-carboxylic acid

A solution of {6R-[2-chloro-6-(tetrahydro-pyran-4-ylamino)-purin-9-yl]-2,2-dimethyl-tetrahydro-(3aR,6aR)-furo[3,4-d][1,3]dioxol-4R-yl}-methanol (2.5g) in ethyl acetate (90ml) was treated with saturated aqueous sodium bicarbonate solution (60ml) and the biphasic mixture stirred rapidly at 0°C. After stirring at 0°C for 5 min, potassium bromide (70mg) was added followed by 2,2,6,6-tetramethyl-1-piperidinyloxy, free radical (TEMPO) (4.6mg). A freshly prepared solution of sodium bicarbonate (185mg) in aqueous sodium hypochlorite (3.2ml) and water was added dropwise to the cooled, stirred mixture over 15 min. The mixture was stirred for a further 20 min at 0°C. Two further additions were made of potassium bromide, TEMPO, and the freshly prepared sodium bicarbonate/ aqueous sodium hypochlorite solution same quantities as before, followed each time by stirring at 0°C for 15-20min. The mixture was poured into ethyl acetate (400ml), shaken with sodium sulphite (10g), diluted with water (300ml), shaken, and the organic and aqueous layers separated. The aqueous layer was acidified to pH 1-2 with 2N hydrochloric acid solution and extracted with ethyl acetate (2x 300ml). The organic layers were combined with those from a second, identical reaction, and evaporated in vacuo to give the product as a cream foam (4.47g).

LC/MS (System B) Rt 2.81 min.
Mass spectrum m/z 440 [MH^+].

Intermediate 7

(3aS,4S,6R,6aR)-6-[2-Chloro-6-(tetrahydro-pyran-4-ylamino)-purin-9-yl]-2,2-dimethyl-tetrahydro-furo[3,4-d][1,3]dioxole-4-carboxylic acid N'-(2,2-dimethyl-propionyl)-hydrazide

Diisopropylethylamine (0.487ml) was added to a stirred solution of (3aS,4S,6R,6aR)-6-[2-chloro-6-(tetrahydro-pyran-4-ylamino)-purin-9-yl]-2,2-dimethyl-tetrahydro-furo[3,4-d][1,3]dioxole-4-carboxylic acid (350mg) in dry tetrahydrofuran (8ml) at 0°C under nitrogen. After 5 min pivaloyl chloride (0.098ml) was added and the mixture was stirred at 0°C for 2.5h. 2,2-Dimethyl-propionic acid hydrazide was added in tetrahydrofuran (2ml) at 0°, and stirring was continued at 0-22°C overnight. The mixture was concentrated in vacuo and partitioned between ethyl acetate (2x30ml) and saturated aqueous sodium bicarbonate (30ml). The organic layers were washed with brine (50ml), dried ($MgSO_4$) and evaporated in vacuo. The residue was azeotroped with dichloromethane (10ml) to give the title compound as a cream solid (357mg).
LC/MS (System B) R_t 2.76 min.
Mass spectrum *m/z* 538 [MH^+].

Intermediate 8

{9-[6S-(5-tert-Butyl-[1,3,4]oxadiazol-2-yl)-2,2-dimethyl-tetrahydro-(3aR,6aS)-furo[3,4-d][1,3]dioxol-4R-yl]-2-chloro-9H-purin-6-yl}-(tetrahydro-pyran-4-yl)-amine

(3aS,4S,6R,6aR)-6-[2-Chloro-6-(tetrahydro-pyran-4-ylamino)-purin-9-yl]-2,2-dimethyl-tetrahydro-furo[3,4-d][1,3]dioxole-4-carboxylic acid N'-(2,2-dimethyl-propionyl)-hydrazide (150mg) was dissolved in N,N-dimethylformamide (1.2ml) and the solution cooled to 0°C under nitrogen. To the cooled, stirred solution phosphorous oxychloride (0.039ml) was added. The solution was stirred at 0°C for 1h, and at 22°C for 16h. The mixture was cooled to 0°C, more phosphorous oxychloride (0.026ml) was added, and the mixture was stirred at 0°C for 1h, and at 22°C for 20h. The mixture was partially evaporated in vacuo, and partitioned

between ethyl acetate (2x30ml) and aqueous sodium bicarbonate (30ml). The organic layers were dried ($MgSO_4$) and concentrated in vacuo to give a yellow oil. Purification by flash chromatography on silica gel, eluting with 30-100% ethyl acetate in cyclohexane, gave the title compound (60mg).

LC/MS (System A) R_t 4.41 min.

Mass Spectrum *m/z* 520 [MH^+].

Example 8

(2S,3S,4R,5R)-2-(5-tert-Butyl-[1,3,4]oxadiazol-2-yl)-5-[2-chloro-6-(tetrahydro-pyran-4-ylamino)-purin-9-yl]-tetrahydro-furan-3,4-diol formate

{9-[6S-(5-tert-Butyl-[1,3,4]oxadiazol-2-yl)-2,2-dimethyl-tetrahydro-(3aR,6aS)-furo[3,4-d][1,3]dioxol-4R-yl]-2-chloro-9H-purin-6-yl}-(tetrahydro-pyran-4-yl)-amine (60mg) was dissolved in 10:1 trifluoroacetic acid:water (2ml) and the mixture was stirred at 0°C for 1h, and at 22°C for 4h. The mixture was evaporated in vacuo, and azeotroped with toluene (2x6ml). The residue was purified by preparative HPLC (gradient profile 5-90% (ii) over 18.5 min) to give the title compound as a white solid (37mg).

LC/MS (System A) R_t 3.86min

Mass spectrum *m/z* 480 [MH^+]

Experimental details for route (C)

Intermediate 9

(3aS,4S,6R,6aR)-6-(6-Cyclopentylamino-purin-9-yl)-2,2-dimethyl-tetrahydro-furo[3,4-d][1,3]dioxole-4-carboxylic acid methyl ester

A solution of (3aS,4S,6R,6aR)-6-(6-cyclopentylamino-purin-9-yl)-2,2-dimethyl-tetrahydro-furo[3,4-d][1,3]dioxole-4-carboxylic acid (3.018g) and 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (2.66g) in methanol (120ml) was heated under reflux for 17h. The resulting mixture was concentrated in vacuo and the residue dissolved in ethyl acetate (150ml). The solution was washed with 0.5M

aqueous citric acid solution (3x25ml) and brine (50ml), dried (magnesium sulphate), and evaporated in vacuo to give a white foam. Purification by column chromatography on silica gel, eluting with ethyl acetate:cyclohexane (1:1), gave the title compound as a white solid (2.32g).

TLC SiO_2 (CH_2Cl_2:MeOH:880NH_3 94:6:1) R_f = 0.62

Intermediate 10

(3aS,4S,6R,6aR)-6-(6-Cyclopentylamino-purin-9-yl)-2,2-dimethyl-tetrahydro-furo[3,4-d][1,3]dioxole-4-carboxylic acid hydrazide

A mixture of (3aS,4S,6R,6aR)-6-(6-cyclopentylamino-purin-9-yl)-2,2-dimethyl-tetrahydro-furo[3,4-d][1,3]dioxole-4-carboxylic acid methyl ester (0.48 g) and hydrazine hydrate (0.29 ml) in methanol (10 ml) was heated at reflux for 28h. After cooling to room temperature, the mixture was concentrated in vacuo and the residue evaporated twice with dichloromethane (2 x 20 ml) to give the title compound as a white solid (0.49g).

NMR (DMSO) 9.4 (1H, brs, NH), 8.32 (1H, s, CH), 8.20 (1H, s, CH), 7.90 (1H, brd, NH), 6.35 (1H, brs, CH), 5.28 (2H, brm, 2 x CH), 4.65 (1H, brs, CH), 4.50 (1H, brm, CH), 4.20 (2H, brs, NH2), 2.0-1.5 (11H, 2xm + s, 4 x CH_2 + CH_3)

Intermediate 11

Cyclopentyl-[9-(2,2-dimethyl-6S-[1,3,4]oxadiazol-2-yl-tetrahydro-(3aR,6aS)-furo[3,4-d][1,3]dioxol-4R-yl)-9H-purin-6-yl]-amine

A mixture of (3aS,4S,6R,6aR)-6-(6-cyclopentylamino-purin-9-yl)-2,2-dimethyl-tetrahydro-furo[3,4-d][1,3]dioxole-4-carboxylic acid hydrazide (0.5g) and triethylorthoformate (5 ml, 4.45g) was heated at reflux for 48h; on cooling, the solution was evaporated to give a brown oil. Purification by flash chromatography on silica gel, eluting with ethyl acetate: cyclohexane (3:1), afforded the title compoundas a cream foam (0.157 g).

TLC SiO_2 (Ethyl acetate:cyclohexane 3:1) R_f = 0.17

Example 15

(2R,3R,4S,5S)-2-(6-Cyclopentylamino-purin-9-yl)-5-[1,3,4]oxadiazol-2-yl-tetrahydro-furan-3,4-diol

Trifluoroacetic acid (1.5 ml) and water (0.15 ml) were added to cyclopentyl-[9-(2,2-dimethyl-6S-[1,3,4]oxadiazol-2-yl-tetrahydro-(3aR,6aS)-furo[3,4-d][1,3]dioxol-4R-yl)-9H-purin-6-yl]-amine (0.157 g) at 0°C and the mixture was stirred for 2 h. The resulting solution was poured into 8% aqueous sodium bicarbonate solution (10 ml) and extracted with ethyl acetate (4 x 20 ml); the organic layers were dried ($MgSO_4$), filtered and evaporated to dryness to give a pale cream foam (0.148 g). Methanol (20 ml) was added and the solid filtered off to afford the title compound as a white solid (0.46 g).

TLC SiO_2 (Ethyl acetate) R_f = 0.13

Analysis Found: C, 50.77; H, 5.14; N, 25.53%
$C_{16}H_{19}N_7O_4$. 0.2MeOH. 0.1H_2O requires: C 50.99; H, 5.3; N, 25.7%

Experimental details for route (D)

Intermediate 12
(3aS,4S,6R,6aR)-6-(6-Chloro-purin-9-yl)-2,2-dimethyl-tetrahydro-furo[3,4-d][1,3]dioxole-4-carboxylic acid (2-oxo-butyl)-amide

A solution of (3aS,4S,6R,6aR)-6-(6-chloro-purin-9-yl)-2,2-dimethyl-tetrahydro-furo[3,4-d][1,3]dioxole-4-carboxylic acid (1.3g), in dry tetrahydrofuran (30ml) was cooled to 3°C before triethylamine (1.07ml) was added. After stirring for 15 min at 3°C, trimethylacetyl chloride (0.56ml) was added and the suspension stirred for 40 min at 3°C. This suspension was added to a stirred mixture of the 2-oxobutylamine hydrochloride in acetonitrile (50ml) containing triethylamine (2.3ml). The mixture was allowed to warm to room temperature, stirred overnight, and partitioned between ethyl acetate (150ml) and 10% aqueous sodium chloride (100ml). The separated aqueous phase was further extracted with ethyl acetate (2x100ml) and the combined organic extracts were washed with brine (70ml), dried and concentrated in vacuo to give a dark red gum (1.83g). Purification by chromatography on silica gel (Merck 7734), eluting with

dichloromethane:ethanol:880 ammonia (250:8:1) gave the title compound as a yellow- brown foam (1.11g).

NMR δ ($CDCl_3$) 8.68 (1H,s,CH), 8.27 (1H,s,CH), 6.73 (1H,brt,NH), 6.30 (1H,d,CH), 5.64 (1H,dd,CH), 5.46 (1H,dd,CH), 4.80 (1H,d,CH), 3.76 (2H,ABX,CH_2), 2.26 (2H,q,CH_2), 1.65 (3H,s,-CH_3), 1.42 (3H,s,-CH_3), 0.99 (3H,t,CH_3).

Intermediate 13

6-Chloro-9-[6S-(5-ethyl-oxazol-2-yl)-2,2-dimethyl-tetrahydro-(3aR,6aS)-furo[3,4-d][1,3]dioxol-4R-yl]-9H-purine

Phosphorous oxychloride (1.43g) was added to a stirred solution of (3aS,4S,6R,6aR)-6-(6-chloro-purin-9-yl)-2,2-dimethyl-tetrahydro-furo[3,4-d][1,3]dioxole-4-carboxylic acid (2-oxo-butyl)-amide (1.05g), in acetonitrile (60ml). The solution was stirred at reflux for 5.5h before standing at room temperature overnight. Stirring was continued at reflux for a further 4.5h, and the mixture was cooled and partitioned between ethyl acetate (150ml) and 8% aqueous sodium bicarbonate (100ml). The separated aqueous phase was further extracted with ethyl acetate (1x100ml) and the combined organic extracts were dried and concentrated in vacuo to give a red gum (1.8g). Purification by chromatography on silica gel (Merck 7734), eluting with dichloromethane:ethanol:ammonia (250:8:1) gave the title compound as a yellow gum (0.86g).

TLC SiO_2 (CH_2Cl_2:EtOH:880NH_3 100:8:1) R_f = 0.5.

Intermediate 14

(2R,3R,4S,5S)-2-(6-Chloro-purin-9-yl)-5-(5-ethyl-oxazol-2-yl)-tetrahydro-furan-3,4-diol

To cooled (0°) 6-chloro-9-[6S-(5-ethyl-oxazol-2-yl)-2,2-dimethyl-tetrahydro-(3aR,6aS)-furo[3,4-d][1,3]dioxol-4R-yl]-9H-purine (0.85g) was added a cold (0°C) mixture of trifluoroacetic acid (8.2ml) and water (0.8ml). The mixture was stirred at 0°C for 5h before being stored in the refrigerator overnight. The mixture was concentrated in vacuo to give a yellow residue which was azeotroped with dichloromethane:ethanol:ammonia (75:8:1) (3x40ml) to give a

yellow liquid (4ml). This was diluted with ethanol (5ml) and purified by chromatography on silica gel (Merck 7734), eluting with dichloromethane:ethanol:ammonia (100:8:1) to (50:8:1) to give the title diol as a pale yellow solid (0.355g).

NMR δ (DMSO) 9.00 (1H,s,CH), 8.85 (1H,s,CH), 6.99 (1H,fine t,CH), 6.1-5.9 (2H,2xbrs,2xOH), 5.05 (1H,d,CH), 4.89 (1H,t,CH), 4.70 (1H,t,CH), 2.7 (2H,dq,CH_2), 1.20 (3H,t,CH_3).

Example 16

(2S,3S,4R,5R)-2-(5-Ethyl-oxazol-2-yl)-5-[6-(tetrahydro-pyran-4-ylamino)-purin-9-yl]-tetrahydro-furan-3,4-diol

To a solution of (2R,3R,4S,5S)-2-(6-chloro-purin-9-yl)-5-(5-ethyl-oxazol-2-yl)-tetrahydro-furan-3,4-diol (0.19g), in isopropanol (15ml) was added diisopropylethylamine (0.3ml) and 4-aminotetrahydropyran hydrochloride (0.135g). After stirring at reflux for 16h, further diisopropylethylamine (0.2ml) and 4-aminotetrahydropyran hydrochloride (60mg) were added. Stirring was continued at reflux for a further 20h before the mixture was cooled and concentrated in vacuo to give a yellow gum (0.8g). Purification by chromatography on silica gel (Merck 7734) with dichloromethane:ethanol:ammonia (250:8:1) – (100:8:1), gave the title compound, as a white foam (0.182g).

Mass spectrum *m/z* 417 [MH^+]

NMR δ (CDCl3) 8.27 (1H,s,CH), 8.13 (1H,s,CH), 6.72 (1H,s,CH), 6.6-6.2 (1H,vbrs,-OH), 6.21 (1H,d,CH), 5.98 (1H,brd,NH), 5.31 (1H,d,CH), 4.79 (2H,m,2xCH), 4.40 (1H,brs,CH), 4.02 (2H,brd,2xCH equatorial), 3.57 (2H,t,2xCH axial), 2.66 (2H,q,CH_2), 2.07 (2H,brd,2xCH equatorial), 1.63 (2H,brq,2xCH axial), 1.23 (3H,t,CH_3).

Experimental details for route (E)

Example 17

(2S,3S,4R,5R)-2-(6-Cyclopentylamino-purin-9-yl)-5-(5-cyclopropyl-[1,3,4]thiadiazol-2-yl)-tetrahydro-furan-3,4-diol

Cyclopropanecarboxylic acid N'-[6R-(6-cyclopentylamino-purin-9-yl)-2,2-dimethyl-tetrahydro-(3aS,6aR)-furo[3,4-d][1,3]dioxole-4S-carbonyl]-hydrazide (12mg) was heated at 80°C with Lawesson's reagent (19mg) in acetonitrile (2ml) for 8h. Further Lawesson's reagent (40mg) was added, and the mixture heated at 70°C for 16h. The solvent was evaporated and the residue purified by chromatography on silica gel (Varian Bondelut cartridge) eluting with ethyl acetate:cyclohexane 20:80 – 100:0 and ethyl acetate:methanol 98:2 – 95:5, to give the protected product (31mg). This material was treated with trifluoroacetic acid (1ml) and water (0.1ml) and the solution allowed to stand at 4°C overnight (19h). The mixture was poured into ice cold aqueous sodium bicarbonate (15ml) and extracted with ethyl acetate (3x15ml). The organic layers were washed with brine, dried ($MgSO_4$) and evaporated in vacuo to give a colourless gum. Purification by automated HPLC (gradient profile 30-60% (ii) over 20 min) gave the title compound (1.33mg).

LC/MS (System A) R_t 4.0 min
Mass spectrum *m/z* 430 [MH^+].

Experimental details for route (F)

Intermediate 15
(3aS,4S,6R,6aR)-6-(6-Isopropylamino-purin-9-yl)-2,2-dimethyl-tetrahydro-furo[3,4-d][1,3]dioxole-4-carboxylic acid

A mixture of (3aS,4S,6R,6aR)-6-(6-chloro-purin-9-yl)-2,2-dimethyl-tetrahydro-furo[3,4-d][1,3]dioxole-4-carboxylic acid (5.82g) and isopropyl amine (7.27 ml) in isopropanol (20 ml) was heated under reflux for 40h, cooled to room temperature and concentrated in vacuo. The resulting residue was partitioned between ethyl acetate (75 ml) and citric acid (0.5M, 75 ml). The layers were separated, and the organic phase washed with citric acid solution (2 x 50 ml). The combined organic extracts were washed with water (50 ml) and brine (80 ml), dried ($MgSO_4$), filtered and concentrated in vacuo to afford the title compound as a light brown foam (4.49 g).

TLC SiO_2 (ethyl acetate) R_f = 0.35

Intermediate 16

(3aS,4S,6R,6aR)-6-(6-Isopropylamino-purin-9-yl)-2,2-dimethyl-tetrahydro-furo[3,4-d][1,3]dioxole-4-carboxylic acid methyl ester

A mixture of (3aS,4S,6R,6aR)-6-(6-isopropylamino-purin-9-yl)-2,2-dimethyl-tetrahydro-furo[3,4-d][1,3]dioxole-4-carboxylic acid (4.82 g) and 2-ethoxy-N-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ, 3.36 g) in methanol (150 ml) was heated under reflux for 60h. After cooling to room temperature, the solution was concentrated in vacuo and the resulting residue partitioned between ethyl acetate (100 ml) and citric acid solution (0.5M, 75 ml). The aqueous layer was extracted with ethyl acetate (4 x 25 ml) and the combined organic extracts were washed with water (50 ml) and brine (75 ml), dried ($MgSO_4$), filtered and concentrated in vacuo. The resulting residue was purified by flash chromatography on silica gel, eluting with ethyl acetate: cyclohexane (1:1) to afford the title compound as a white solid (3.76 g).
TLC SiO_2 (ethyl acetate:cyclohexane 1:1) R_f = 0.20.

Intermediate 17

(3aS,4S,6R,6aR)-6-(6-Isopropylamino-purin-9-yl)-2,2-dimethyl-tetrahydro-furo[3,4-d][1,3]dioxole-4-carboxylic acid hydrazide

A mixture of (3aS,4S,6R,6aR)-6-(6-isopropylamino-purin-9-yl)-2,2-dimethyl-tetrahydro-furo[3,4-d][1,3]dioxole-4-carboxylic acid methyl ester (3.76 g) and hydrazine hydrate (1.26 ml) in methanol (140 ml) was heated under reflux for 48h. After cooling to room temperature, the mixture was concentrated in vacuo and the residue triturated with ethyl acetate to afford the title compound as a white solid (3.3 g).
Analysis Found: C, 51.5; H, 6.5; N, 23.6%
$C_{16}H_{23}N_7O_4$. 0.4EtOAc requires: C, 51.0; H, 6.4; N, 23.8%

Example 18

(2R,3R,4S,5R)-2-(6-Isopropylamino-purin-9-yl)-5-(5-methyl-4H-[1,2,4]triazol-3-yl)-tetrahydro-furan-3,4-diol trifluoroacetate

A mixture of (3aS,4S,6R,6aR)-6-(6-isopropylamino-purin-9-yl)-2,2-dimethyl-tetrahydro-furo[3,4-d][1,3]dioxole-4-carboxylic acid hydrazide (0.5 g), ethylacetimidate hydrochloride (0.24 g) and triethylamine (0.55 ml) in ethanol (10 ml) was heated under reflux for 72h and cooled to room temperature. The solvent was evaporated in vacuo and the residue purified by flash chromatography on silica gel (Merck 9385), eluting with ethyl acetate: methanol (9:1), to afford a white solid (0.37 g), which was treated with trifluoroacetic acid (3.6 ml) and water (0.36 ml); the mixture stirred at 0°C for 6h. The resulting solution was evaporated to dryness, toluene was added and the mixture re-evaporated to dryness. The resulting residue was triturated with ethyl acetate to afford the title compound as a white solid (0.41 g).

R (DMSO) 8.71 (1H, brs, NH), 8.40-8.20 (2H, s + brs 2 x CH), 6.11 (1H, d, CH), 5.00 (1H, d, CH), 4.73 (1H, t, CH), 4.44 (2H, t + brm, 2 xCH), 2.42 (3H, s, CH_3), 1.27 (6H, d, 2 x CH_3)

Analysis Found: C, 42.9; H, 4.45; N, 23.5%
$C_{15}H_{20}N_8O_3$ requires: C, 43.0; H, 4.4; N, 23.6%

Experimental details for route (G).

Intermediate 18
6-Chloro-9-[6S-(3-cyclopropyl-[1,2,4]oxadiazol-5-yl)-2,2-dimethyl-tetrahydro-(3aR,6aS)-furo[3,4-d][1,3]dioxol-4R-yl]-9H-purine

A suspension of (3aS,4S,6R,6aR)-6-(6-chloro-purin-9-yl)-2,2-dimethyl-tetrahydro-furo[3,4-d][1,3]dioxole-4-carboxylic acid (4.17 g) in anhydrous tetrahydrofuran (80 ml) was cooled under nitrogen to 5°C. To the suspension was added diisopropylethylamine (4.68 ml). Pivaloyl chloride (1.65 ml) was added after 10 min, and the mixture was stirred at 0°C for 1 h, and allowed to warm to room temperature over 1 h. The mixture was again cooled to 5°C, cyclopropylamidoxime (1.47 g) was added dropwise, the cooling bath was removed and stirring was continued at 22°C for 18 h. The diisopropylethylamine hydrochloride was filtered off and washed with tetrahydrofuran (100 ml). The filtrate was heated at reflux for 10 h, cooled and concentrated in vacuo to give a

residue which was purified by chromatography on silica gel (Varian Mega Bondelut cartridge), eluting with ethyl acetate:cyclohexane (3:1), to afford the title compound as a white solid (1.99 g).
LC/MS (System B): R_t = 2.91 min
Mass spectrum *m/z* 405 (MH^+)

Intermediate 19
(2R,3R,4S,5S)-2-(6-Chloro-purin-9-yl)-5-(3-cyclopropyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol

A solution of 6-chloro-9-[6S-(3-cyclopropyl-[1,2,4]oxadiazol-5-yl)-2,2-dimethyl-tetrahydro-(3aR,6aS)-furo[3,4-d][1,3]dioxol-4R-yl]-9H-purine (1.99g) in a cold mixture of trifluoroacetic acid:water (9:1; 25 ml) was kept at 4°C for 20 h. The resulting solution was basified in an ice bath with a saturated solution of sodium bicarbonate (200 ml), extracted with ethyl acetate (3 x 70 ml) and the extracts dried ($MgSO_4$) and concentrated in vacuo. The resulting brown oil was purified by chromatography on silica gel (Varian Mega Bondelut cartridge), eluting with dichloromethane:methanol (10:1) to afford the title compound (1.29 g) as a white solid.
LC/MS (System B): R_t = 2.42 min
Mass spectrum *m/z* 365 (MH^+)

Example 19
(2S,3S,4R,5R)-2-(3-Cyclopropyl-[1,2,4]oxadiazol-5-yl)-5-[6-(2S-hydroxy-cyclopent-(S)-ylamino)-purin-9-yl]-tetrahydro-furan-3,4-diol

To a solution of (2R,3R,4S,5S)-2-(6-chloro-purin-9-yl)-5-(3-cyclopropyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol (50 mg) in isopropanol (5 ml) was added diisopropylethylamine (0.072 ml) and trans-(1S,2S)-2-aminocyclopentanol hydrochloride (37.8 mg). The mixture was heated at reflux for 48 h, cooled to room temperature and concentrated to dryness in vacuo to give a residue which was purified by solid phase extraction (5 g, Varian Mega Bondelut cartridge, aminopropyl bonded phase, eluting with (i) $CHCl_3$, (ii) ethyl acetate:cyclohexane (1:1), (iii) ethyl acetate, (iv) dichloromethane, (v)

dichloromethane:methanol (20:1), (vi) dichloromethane:methanol (10:1) and (vii) methanol to afford the title compound (47.3 mg).
LC/MS (System B): R_t = 2.37 min
Mass spectrum *m/z* 430 (MH^+)

Experimental details for route (H)

Intermediate 20
4-[9-(6S-Carboxy-2,2-dimethyl-tetrahydro-(3aR,6aS)-furo[3,4-d][1,3]dioxol-4R-yl)-9H-purin-6-ylamino]-piperidine-1-carboxylic acid ethyl ester

A mixture of ethyl-4-amino-piperidinecarboxylate (1.80 ml), (3aS,4S,6R,6aR)-6-(6-chloro-purin-9-yl)-2,2-dimethyl-tetrahydro-furo[3,4-d][1,3]dioxole-4-carboxylic acid (2.0 g) and diisopropylethylamine (2.74 ml) was heated at reflux in isopropanol (100 ml) for 70 h. After cooling to room temperature the mixture was concentrated in vacuo. Water (100 ml) was added to the residue and the mixture acidified to pH 4 (citric acid). The mixture was rapidly extracted with dichloromethane (3 x 50 ml) and the extracts dried ($MgSO_4$) and concentrated in vacuo to afford the title compound as a yellow solid (2.56 g).
LC/MS (System B): R_t = 2.62 min
Mass spectrum *m/z* 477

Intermediate 21
4-[9-(6S-Carbamoyl-2,2-dimethyl-tetrahydro-(3aR,6aS)-furo[3,4-d][1,3]dioxol-4R-yl)-9H-purin-6-ylamino]-piperidine-1-carboxylic acid ethyl ester

A cooled (0°C) solution of 4-[9-(6S-carboxy-2,2-dimethyl-tetrahydro-(3aR,6aS)-furo[3,4-d][1,3]dioxol-4R-yl)-9H-purin-6-ylamino]-piperidine-1-carboxylic acid ethyl ester (2.56 g) in anhydrous dichloromethane (50 ml) was treated with triethylamine (0.82 ml) and pivaloyl chloride (0.73 ml). Ammonia was bubbled into the solution for 70 min. The mixture was evaporated to dryness in vacuo to give a crude product, which was dissolved in ethyl acetate and washed with water (3 x 70 ml). The extracts were dried ($MgSO_4$) and concentrated in vacuo to afford the title compound as a pale orange solid (1.97 g).
LC/MS (System B): R_t = 2.54 min

Mass spectrum *m/z* 476 (MH^+)

Intermediate 22

4-[9-(6R-Cyano-2,2-dimethyl-(3aR,6aR)-tetrahydro-furo[3,4-d][1,3]dioxol-4R-yl)-9H-purin-6-ylamino]-piperidine-1-carboxylic acid ethyl ester

A solution of 4-[9-(6S-carbamoyl-2,2-dimethyl-tetrahydro-(3aR,6aS)-furo[3,4-d][1,3]dioxol-4R-yl)-9H-purin-6-ylamino]-piperidine-1-carboxylic acid ethyl ester (1.97 g) in anhydrous acetonitrile (40 ml) was treated with 4-dimethylaminopyridine (1.01 g). The mixture was cooled to 0°C and phosphorus oxychloride (1.93 ml) added dropwise. The mixture was allowed to warm to room temperature and stirred at this temperature for 1 h then heated at reflux for 7 h. After cooling, the mixture was evaporated to dryness in vacuo to give the crude product which was dissolved in water (50 ml) and extracted with ethyl acetate (3 x 70 ml). The extracts were concentrated in vacuo to afford the title compound as a pale orange solid (1.91 g).

LC/MS (System A): R_t = 4.09 min

Mass Spectrum *m/z* 458 (MH^+)

Intermediate 23

4-[9-[6R-(N-Hydroxycarbamimidoyl)-2,2-dimethyl-tetrahydro-(3aR,6aR)-furo[3,4-d][1,3]dioxol-4R-yl]-9H-purin-6-ylamino]-piperidine-1-carboxylic acid ethyl ester

4-[9-(6R-Cyano-2,2-dimethyl-(3aR,6aR)-tetrahydro-furo[3,4-d][1,3]dioxol-4R-yl)-9H-purin-6-ylamino]-piperidine-1-carboxylic acid ethyl ester (1.0 g) and hydroxylamine (50%; 0.29 ml) were heated at reflux in ethanol (25 ml) for 9 h. After cooling, the mixture was concentrated in vacuo and the residue was co-evaporated in toluene (50 ml) to give the title compound as a yellow solid (1.25g).

LC/MS (System A): R_t = 3.82 min

Mass spectrum *m/z* 490 (MH^+)

Intermediate 24

4-{9-[6R-(5-tert-Butyl-[1,2,4]oxadiazol-3-yl)-2,2-dimethyl-tetrahydro-(3aR,6aR)-furo[3,4-d][1,3]dioxol-4R-yl]-9H-purin-6-ylamino}-piperidine-1-carboxylic acid ethyl ester

4-{9-[6R-(N-Hydroxycarbamimidoyl)-2,2-dimethyl-tetrahydro-(3aR,6aR)-furo[3,4-d][1,3]dioxol-4R-yl]-9H-purin-6-ylamino}-piperidine-1-carboxylic acid ethyl ester (1.0 g) was stirred with pivalic acid (15 ml) and pivalic anhydride (0.49 ml) at ambient temperature for 2 h, then heated at reflux for 9 h. After cooling, the residue was treated with a saturated solution of sodium bicarbonate (100 ml) and extracted with ethyl acetate (4 x 100 ml). The extracts were dried ($MgSO_4$) and concentrated in vacuo. To the residue was added diethylether (100 ml). A brown precipitate was formed and filtered off, and the filtrate was concentrated in vacuo to afford a crude product. Purification by chromatography on silica gel (Varian Mega Bondelut cartridge) eluting with ethyl acetate afforded the title compound as a pale orange oil (0.360g).
LC/MS (System B):R_t = 3.13 min
Mass spectrum *m/z* 557 (MH^+)

Example 26

4-{9-[5R-(5-tert-Butyl-[1,2,4]oxadiazol-3-yl)-3R,4S-dihydroxy-tetrahydro-furan-2R-yl]-9H-purin-6-ylamino}-piperidine-1-carboxylic acid ethyl ester

A solution of 4-{9-[6R-(5-tert-butyl-[1,2,4]oxadiazol-3-yl)-2,2-dimethyl-tetrahydro-(3aR,6aR)-furo[3,4-d][1,3]dioxol-4R-yl]-9H-purin-6-ylamino}-piperidine-1-carboxylic acid ethyl ester (360 mg) in a cold mixture of trifluoroacetic acid:water (9:1; 5 ml) was cooled to 0°C for 20 h. The resulting solution was neutralised with an ice-cold saturated solution of sodium bicarbonate (70 ml), extracted with ethyl acetate (3 x 50 ml) and the extracts dried ($MgSO_4$) and concentrated in vacuo. Preparative hplc was carried out on a Supelcosil LC-ABZ column (size 21.2mm x 10cm) operating at 8ml/min (eluents were A: 0.1% trifluoroacetic acid /water, B: 0.01% trifluoroacetic acid in 95:5 acetonitrile/water) (gradient profile 15 – 95% B over 25 min), to afford the title compound as a white solid (6.9 mg).
LC/MS (System B): R_t = 2.76 min
Mass spectrum *m/z* 517 (MH^+)

Experimental Details for route (I)

Intermediate 25
(3aS,4S,6R,6aR)-6-Methoxy-2,2-dimethyl-tetrahydro-furo[3,4-d][1,3]dioxole-4-carboxylic acid methoxy-methyl-amide

(3aS,4S,6R,6aR)-Methoxy-2,2-dimethyl-tetrahydro-furo[3,4-d][1,3]dioxole-4-carboxylic acid (11g) was dissolved in dichloromethane (100ml) and carbonyldi-imidazole (8.47g) added portionwise over 10 min at 22°C and the solution stirred at 22°C for 0.5h. N,O-Dimethylhydroxylamine hydrochloride (12.5g) was dissolved in water (50ml) and 10N sodium hydroxide (20ml) added, and the solution extracted with dichloromethane (3x50ml). The dichloromethane extracts were dried (Na_2SO_4) and filtered, and the solution added to the above solution. After stirring for 3 days, the solution was washed with 0.5M citric acid (200ml), 8% sodium bicarbonate (200ml), dried (Na_2SO_4) and evaporated in vacuo to give the title compound as a colourless oil (14.2g).
TLC: SiO_2 (ether) R_f = 0.33.

Intermediate 26
1-(6R-Methoxy-2,2-dimethyl-tetrahydro-(3aS,6aR)-furo[3,4-d][1,3]dioxol-4S-yl)-4,4-dimethyl-pent-2-yn-1-one

3,3-Dimethyl-1-butyne (10g) in THF (90ml) was added slowly to a 3.0M solution of methylmagnesium chloride in THF (50ml) under nitrogen at 0-5°C, and stirred at 0-5°C for 5h. (3aS,4S,6R,6aR)-6-Methoxy-2,2-dimethyl-tetrahydro-furo[3,4-d][1,3]dioxole-4-carboxylic acid methoxy-methyl-amide (14.17g) was added in THF (20ml) over 20 min at 0-5°C, and the solution stirred at 0-5°C for 2h. The reaction mixture was quenched with 30% ammonium chloride (150ml) and 2M hydrochloric acid (15ml) and extracted with ethyl acetate (2x150ml). The combined organic phases were dried (Na_2SO_4) and evaporated *in vacuo*, and the residue purified by flash chromatography over silica (150g) eluting with cyclohexane-diethyl ether (2:1) to afford the title compound as a colourless solid (4.01g).
TLC: SiO_2 (ether) R_f = 0.55

Intermediate 27

1-(6R-Methoxy-2,2-dimethyl-tetrahydro-(3as,6aR)-furo[3,4-d][1,3]dioxol-4S-yl)-4,4-dimethyl-pentane-1,3-dione-3-oxime

1-(6R-Methoxy-2,2-dimethyl-tetrahydro-(3aS,6aR)-furo[3,4-d][1,3]dioxol-4S-yl)-4,4-dimethyl-pent-2-yn-1-one (573mg) was dissolved in methanol (6ml) and 50% aqueous hydroxylamine (0.19ml) added. After standing at 23°C for 5h, the solution was concentrated *in vacuo*, diluted with water (10ml) and extracted with ethyl acetate (2x15ml). The extracts were dried (Na_2SO_4) and evaporated *in vacuo* to afford the title compound as a colourless oil (0.635g).
TLC: SiO_2 (cyclohexane-Et_2O 3:2) R_f = 0.16

Intermediate 28

Acetic acid 4R-acetoxy-2S-(3-tert-butyl-isoxazol-5-yl)-5-methoxy-tetrahydro-furan-3R-yl ester

1-(6R-Methoxy-2,2-dimethyl-tetrahydro-(3aS,6aR)-furo[3,4-d][1,3]dioxol-4S-yl)-4,4-dimethyl-pentane-1,3-dione 3-oxime (632mg) was dissolved in methanol (15ml) and conc. hydrochloric acid (1ml) added. The resulting solution was heated under reflux under nitrogen for 20h, cooled and evaporated *in vacuo*. The residue was dissolved in pyridine (10ml) and 4-dimethylaminopyridine (1mg) and acetic anhydride (2ml) added. The solution was allowed to stand at 22°C /3h, and the solvents removed *in vacuo*. The residue was dissolved in ethyl acetate (100ml), washed with 8% sodium bicarbonate (50ml), dried (Na_2SO_4) and evaporated in vacuo to give the title compound as a pale yellow gum (575mg).
Mass spectrum m/z 342 (MH^+)

Intermediate 29

Acetic acid 4R-acetoxy-5S-(3-tert-butyl-isoxazol-5-yl)-2R-(6-chloro-purin-9-yl)-tetrahydro-furan-3R-yl ester

6-Chloropurine (1.36g), toluene (20ml) and hexamethyldisilazane (10ml) were heated under reflux under nitrogen for 2h, cooled, and evaporated *in vacuo*. The residue was co-evaporated with dry toluene (12ml) and taken into dry

acetonitrile (20ml) and acetic acid 4R-acetoxy-2S-(3-tert-butyl-isoxazol-5-yl)-5-methoxy-tetrahydrofuran-3R-yl ester (1.01g) and trimethylsilyl trifluoromethanesulfonate (1.8ml) added, and the solution heated under reflux under nitrogen for 5h. The solution was cooled and poured into 8% sodium bicarbonate (150ml) and extracted with ethyl acetate (2x100ml). The extracts were combined, dried (Na_2SO_4) and evaporated in vacuo. The residue was purified by flash chromatography over silica (200g) eluting with cyclohexane-ether (1:1-1:4) to afford the title compound as a colourless foam (0.953g).
LCMS (system A) R_t = 4.35 min.

Example 27
(2S,3S,4R,5R)-2-(3-tert-Butyl-isoxazol-5-yl)-5-[6-(2S-hydroxy-cyclopent-(S)-ylamine)-purin-9-yl]-tetrahydro-furan-3,4-diol

Acetic acid 4R-acetoxy-5S-(3-tert-butyl-isoxazol-5-yl)-2R-(6-chloro-purin-9-yl)-tetrahydro-furan-3R-yl ester (70mg) and trans-(1S,2S)-2-aminocyclopentanol hydrochloride (62mg) were dissolved in isopropanol (10ml) and di-isopropylethylamine (0.16ml) added, and the solution heated under reflux for 17h. The solvent was evaporated *in vacuo* and the residue dissolved in saturated methanolic ammonia (7ml) and allowed to stand for 3h. The solvent was removed *in vacuo* and the residue purified by chromatography over silica (5g) eluting with ethyl acetate-methanol (10:1). Further purification by autoprep HPLC afforded the *title compound* as a colourless gum (40mg).
LCMS (system A): R_t = 3.81 min
Mass spectrum: m/z 445 (MH^+)

Example 28
(2S,3S,4R,5R)-2-(3-tert-Butyl-isoxazol-5-yl)-5-[6-(tetrahydro-pyran-4-ylamino)-purin-9-yl]-tetrahydro-furan-3,4-diol

Acetic acid 4R-acetoxy-5S-(3-tert-butyl-isoxazol-5-yl)-2R-(6-chloro-purin-9-yl)-tetrahydro-furan-3R-yl ester (70mg) and 4-aminotetrahydropyran hydrochloride (62mg) were dissolved in isopropanol (10ml) and di-isopropylethylamine (0.16ml) added, and the solution heated under reflux for 17h. The solvent was removed in vacuo and the residue dissolved in saturated methanolic ammonia

(7ml), and allowed to stand for 3h. The solvent was removed in vacuo and the residue purified by solid phase extraction (Varian Bondelut aminopropyl bonded silica gel cartridge), eluting with ethyl acetate-methanol (10:1). Further purification by autoprep HPLC gave the title compound as a colourless gum (31mg).

LCMS (system A): R_t = 3.78 min

Mass spectrum m/z 445 (MH^+)

Experimental details for route (J)

Intermediate 30

(E)-3-Dimethylamino-1-(6R-methoxy-2,2-dimethyl-tetrahydro-(3aS,6aR)-furo[3,4-d][1,3]dioxol-4S-yl)-propenone

1-(6R-Methoxy-2,2-dimethyl-tetrahydro-(3aS,6aR)-furo[3,4-d][1,3]diox-4S-yl)-ethanone (0.62g) was dissolved in toluene (25ml) and dimethylformamide dimethyl acetal (5ml) added and the solution heated under reflux under nitrogen for 17h. The solvents were removed in vacuo and the residue purified by flash chromatography over silica (30g) eluting with ethyl acetate to afford the title compound as a yellow gum (0.102g).

Mass spectrum m/z 272 (MH^+)

Intermediate 31

5-(6R-Methoxy-2,2-dimethyl-tetrahydro-(3aR,6aR)-furo[3,4-d][1,3]dioxol-4R-yl)-1H-pyrazole

(E)-3-Dimethylamino-1-(6R-methoxy-2,2-dimethyl-tetrahydro-(3aR,6aR)-furo[3,4-d][1,3]dioxol-4S-yl)-propenone (102mg) was dissolved in methanol (15ml) and hydrazine hydrate (0.5ml) added and the solution heated under reflux for 1.5h. The solvents were removed in vacuo and the residue purified by flash chromatography over silica gel, eluting with diethyl ether to afford the title compound as a colourless gum (47mg).

Mass spectrum m/z 241 (MH^+)

Intermediate 32

Acetic acid 4R-acetoxy-2R-(1-acetyl-1H-pyrazol-3-yl)-5R-methoxy-tetrahydro-furan-3R-yl ester

5-(6R-Methoxy-2,2-dimethyl-tetrahydro-(3aR,6aR)-furo[3,4-d][1,3]dioxol-4R-yl)-1H-pyrazole (1.66g) was dissolved in methanol (120ml), treated with conc. hydrochloric acid (1ml), heated under reflux for 22h, cooled and evaporated in vacuo. The residue was dissolved in pyridine (80ml), acetic anhydride (4ml) added and the solution allowed to stand for 3h. The solvents were removed in vacuo and the residue taken into ethyl acetate (200ml) and washed successively with 0.5M citric acid (100ml), 8% sodium bicarbonate (100ml) and brine (100ml). The organic phase was dried (Na_2SO_4), evaporated in vacuo and the residue purified by flash chromatography over silica gel, eluting with cyclohexane-diethyl ether (2:1-1:1) to afford the title compound as a colourless gum (646mg).
Mass spectrum m/z 327 (MH^+), 344 (MNH_4^+)

Intermediate 33

Acetic acid 4R-acetoxy-5R-(1-acetyl-1H-pyrazol-3-yl)-2R-(6-chloro-purin-9-yl)-tetrahydro-furan-3R-yl ester

6-Chloropurine (1g) was suspended in toluene (40ml), hexamethyldisilazane (10ml) was added, and the mixture was heated under reflux for 1h. After cooling, the solvents were evaporated in vacuo followed by co-evaporation with toluene (10ml). The residue was dissolved in dry acetonitrile (40ml), acetic acid 4R-acetoxy-2R-(1-acetyl-1H-pyrazol-3-yl)-5R-methoxy-tetrahydro-furan-3R-yl ester (645mg), DBU (1ml) and trimethylsilyl trifluoromethanesulfonate (1ml) were added, and the resulting solution was heated under reflux under nitrogen for 3h. The cooled solution was poured into 8% sodium bicarbonate (150ml) and extracted with ethyl acetate (2x100ml). The combined extracts were dried (Na_2SO_4) and evaporated in vacuo to afford a mixture which was purified by flash chromatography over silica gel, eluting with ether-cyclohexane (3:1) to afford the title compound (42mg).
Mass spectrum m/z 449/451 (MH^+)

Intermediate 34

(2R,3R,4S,5R)-2-(6-Chloro-purin-9-yl)-5-(2H-pyrazol-3-yl)-tetrahydro-furan-3,4-diol

Acetic acid 4R-acetoxy-5-(1-acetyl-1H-pyrazol-3-yl)-2R-(6-chloro-purin-9-yl)-tetrahydro-furan-3R-yl ester (42mg) was dissolved in methanol (3ml) and cooled to 0°C. Tert-butylamine (0.2ml) was added and the solution allowed to stand for 25 min. at 0°C. The solvents were removed in vacuo to furnish the title compound (35mg).
Mass spectrum m/z 323/325 (MH^+)

Example 29
(2R,3R,4S,5R)-2-(2H-Pyrazol-3-yl)-5-(6-tetrahydro-pyran-4-ylamino-purin-9-yl)-tetrahydro-furan-3,4-diol

(2R,3R,4S,5R)-2-(6-Chloro-purin-9-yl)-5-(2H-pyrazol-3-yl)-tetrahydro-furan-3,4-diol (35mg) was dissolved in isopropanol (3ml), N,N-di-isopropylethylamine (0.12ml) and tetrahydro-pyran-4-ylamine hydrochloride (46mg) were added, and the resulting solution was heated under reflux under nitrogen for 17h. The solvent was removed in vacuo, the residue dissolved in methanol (10ml), and 8% sodium bicarbonate (3ml) added, followed by silica gel (3g). The solvents were removed in vacuo and the residue added to a flash column of silica gel packed in dichloromethane. Elution with dichloromethane-methanol (4:1) afforded the title compound as a clear viscous gum (5.2mg).
LCMS (system A) R_t = 3.34 min.
Mass spectrum m/z 388 (MH^+)

Experimental details for route (K)

Intermediate 35
(3aS,4S,6R,6aR)-6-(6-Chloropurin-9-yl)-2,2-dimethyl-tetrahydro-furo[3,4-d][1,3]dioxole-4-carboxylic acid methoxy-methyl-amide

(3aS,4S,6R,6aR)-6-(6-Chloro-purin-9-yl)-2,2-dimethyl-tetrahydro-furo[3,4-d][1,3]dioxole-4-carboxylic acid (35.88g) was dissolved in dichloromethane (300ml) and treated with 1,1'-carbonyldiimidazole (20.5g) with ice-cooling. The

solution was stirred at 22°C for 1h, N,O-dimethylhydroxylamine hydrochloride (12.3g) and pyridine (15ml) were added, and stirring was continued at 22°C for 24h. The solution was washed with 0.5M citric acid (250ml) and 8% sodium bicarbonate (200ml), dried (Na_2SO_4) and evaporated in vacuo. The residue was purified by flash chromatography over silica gel, eluting with ethyl acetate to afford the title compound as a colourless solid (26.4g).
LCMS (system A) R_t = 3.77 min
Mass spectrum m/z 384/386 (MH^+)

Intermediate 36
(3aS,4S,6R,6aR)-2,2-Dimethyl-6-(6-thioxo-1,6-dihydro-purin-9-yl)-tetrahydro-furo[3,4-d][1,3]dioxole-4-carboxylic acid methoxy-methyl-amide

(3aS,4S,6R,6aR)-6-(6-Chloro-purin-9-yl)-2,2-dimethyl-tetrahydro-furo[3,4-d][1,3]dioxide-4-carboxylic acid methoxy-methyl-amide (23.3g) was suspended in ethanol (250ml), and treated with sodium hydrogen sulfide (10g). The mixture was stirred under reflux under nitrogen for 3h, cooled and evaporated in vacuo. The residue in water (250ml) was acidified with 0.5M citric acid (ca. 40ml), filtered, and the filtered solid washed with water (250ml) and isopropanol (100ml) and dried in vacuo to afford the title compound as a yellow solid (16.3g).
LC/MS (system A) R_t = 3.53 min
Mass spectrum m/z 382 (MH^+)

Intermediate 37
{9-[6R-(5-Tert-Butyl-2H-pyrazol-3-yl)-2,2-dimethyl-tetrahydro-(3aR,6aR)-furo[3,4-d][1,3]dioxol-4R-yl]-9H-purin-6-yl}-cyclopentylamine

(3aS,4S,6R,6aR)-2,2-Dimethyl-6-(6-thioxo-1,6-dihydro-purin-9-yl)-tetrahydro-furo[3,4-d][1,3]dioxole-4-carboxylic acid methoxy-methyl-amide (1g) was dissolved in N,N-dimethylformamide (DMF) (25ml) with heating and filtered whilst hot. The filtrate was treated with di-isopropylethylamine (0.5ml) and Merrifield resin (chloromethyl form, 2g, 0.8mmol/g, 1% cross-linked) and the mixture shaken for 24h. The mixture was filtered and the filtered resin washed with DMF (2x15ml), dichloromethane (2x15ml) and ether (3x15ml). The above resin was added to a solution of 3,3-dimethyl-1-butynylmagnesium chloride

(prepared by treating 3,3-dimethyl-1-butyne [2ml] with 3.0M methyl magnesium chloride in tetrahydrofuran (THF) [4ml] in THF [25ml] at 22° for 17h) in THF at 0-5°C, and the mixture was stirred at 0-5°C for 6h. 2M Hydrochloric acid (6ml) and THF (12ml) were added, and after 10 min shaking, the resin was filtered and washed with THF (2x15ml) and ether (2x15ml). The resin was re-suspended in DMF (25ml), hydrazine hydrate (2ml) was added, and the mixture was shaken for 17h. The mixture was filtered, washed with DMF (30ml), dichloromethane (2x10ml) and _ ether (3x10ml), re-suspended in dichloromethane (15ml), treated with 3-chloroperoxybenzoic acid (57-81%, 0.50g) and shaken at 22°C for 17h. The resin was filtered off, and washed with dichloromethane (3x10ml) and ether (2x10ml). The residue in THF (10ml) was treated with cyclopentylamine (88 l) and di-isopropylethylamine (0.16ml), and the mixture was shaken at 22°C for 17h. The mixture was filtered, washed with THF-methanol (3:1, 2x10ml), and the filtrate and washings were evaporated in vacuo. Purification by automated preparative HPLC afforded the title compound (20mg).

LC/MS (system A) R_t = 4.48 min

Mass spectrum m/z 468 (MH^+)

Example 30

(2R,3R,4S,5R)-2-(5-tert-Butyl-2H-pyrazol-3-yl)-5-(6-cyclopentylamino-purin-9-yl)-tetrahydro-furan-3,4-diol

{9-[6R-(5-tert-Butyl-2H-pyrazol-3-yl)-2,2-dimethyl-tetrahydro-(3aR,6aR)-furo[3,4-d][1,3]dioxol-4R-yl]-9H-purin-6-yl}-cyclopentylamine (20mg) was dissolved in trifluoroacetic acid-water (9:1, 4ml) and the mixture was allowed to stand at 0-5°C for 17h. The solution was evaporated in vacuo (bath temp <30°C) and quenched with 2M sodium carbonate (15ml). The mixture was extracted with ethyl acetate (2x15ml), and the combined extracts dried (Na_2SO_4) and evaporated in vacuo. The residue was purified by chromatography on silica gel (Varian Bondelut cartridge), eluting with ethyl acetate-methanol (9:1), to afford the title compound as a clear gum (19mg).

LC/MS (system A) R_t = 4.0 min

Mass spectrum m/z 428 (MH^+)

Experimental details for route (L)

Intermediate 38
3-Ethyl-5-(6R-methoxy-2,2-dimethyl-tetrahydro-(3aR,6aR)-furo[3,4-d][1,3]dioxol-4S-yl)-isoxazole

To a stirring mixture of 4R-ethynyl-6R-methoxy-2,2-dimethyl-tetrahydro-(3aR,6aR)-furo[3,4-d][1,3]dioxole [lit. compd.; ref: *Helv. Chim. Acta* **1980**, *63*, 1181-1189.] (0.271g) and phenyl isocyanate (0.328ml) in dry toluene (1.5ml) under nitrogen, was added a mixture of 1-nitropropane (0.134ml) and triethylamine (0.038ml) in dry toluene (1ml) over 5min. A precipitate was formed slowly during the addition. The resultant mixture was heated at between 73°C to 82°C for 18h. The cooled reaction mixture was filtered through silica gel, washed well with ether and then 40% ethyl acetate - cyclohexane. Removal of solvent in vacuo gave a light brown solid (0.487g) which was subjected to flash chromatography on silica gel, eluting with ethyl acetate: cyclohexane 20:80-30:70, to give the title compound as a clear oil (0.329g).

TLC (cyclohexane-ethyl acetate 3:2) R_f = 0.49.

Intermediate 39a Acetic acid 4R,5S-diacetoxy-2S-(3-ethyl-isoxazol-5-yl)-tetrahydro-furan-3R-yl ester and **Intermediate 39b** Acetic acid 4R,5R-diacetoxy-2S-(3-ethyl-isoxazol-5-yl)-tetrahydro-furan-3R-yl ester

A solution of 3-ethyl-5-(6R-methoxy-2,2-dimethyl-tetrahydro-(3aR,6aR)-furo[3,4-d][1,3]dioxol-4S-yl)-isoxazole (0.355g) in a mixture of trifluoroacetic acid (5ml) and water (0.05ml) was stirred at room temperature for 27h and then evaporated in vacuo. The residue was azeotroped with toluene (x3), dissolved in dry dichloromethane (10ml) under nitrogen, and cooled to 0°C. 4-(N,N-dimethylamino)pyridine (0.048g), triethylamine (8.3ml) followed by acetic anhydride (2.49ml) were added. The mixture was stirred at 0° to room temperature overnight. The resultant mixture was evaporated in vacuo to give a brown liquid (1.34g). Purification by flash chromatography on silica gel, eluting with ethyl acetate:cyclohexane 20:80-40:60, afforded acetic acid 4R,5S-diacetoxy-2S-(3-ethyl-isoxazol-5-yl)-tetrahydro-furan-3R-yl ester (0.192g) as a

light brown oil, followed by acetic acid 4R,5R-diacetoxy-2S-(3-ethyl-isoxazol-5-yl)-tetrahydro-furan-3R-yl ester (0.16g) as a light brown oil.

Intermediate 39a SiO_2 TLC (Cyclohexane-ethyl acetate 3:2), R_f = 0.28

Intermediate 39b SiO_2 TLC (Cyclohexane-ethyl acetate 3:2), R_f = 0.22

Intermediate 40

Acetic acid 4R-acetoxy-2R-(2,6-dichloro-purin-9-yl)-5S-(3-ethyl-isoxazol-5-yl)-tetrahydro-furan-3R-yl ester

To a mixture of acetic acid 4R,5S-diacetoxy-2S-(3-ethyl-isoxazol-5-yl)-tetrahydro-furan-3R-yl ester and acetic acid 4R,5R-diacetoxy-2S-(3-ethyl-isoxazol-5-yl)-tetrahydro-furan-3R-yl ester (0.909g) in dry acetonitrile (5ml) at room temperature under nitrogen was added 2,6-dichloropurine (0.779g), DBU (0.692ml) followed by trimethylsilyl triflate (0.99ml). The reaction was stirred at room temperature for 20h, and quenched with saturated aqueous sodium bicarbonate solution (30ml). Extraction with ethyl acetate (3x40ml) gave a brown liquid (3.54g). Purification by flash chromatography on silica gel, eluting with ethyl acetate:cyclohexane 40:60-50:50, gave the title compound as a creamy white foam (0.798g).

TLC SiO_2 (Cyclohexane–ethyl acetate 2:3), R_f = 0.25.

Intermediate 41

Acetic acid 4R-acetoxy-2R-[2-chloro-6-(1S-hydroxymethyl-2-phenyl-ethylamino)-purin-9-yl]-5S-(3-ethyl-isoxazol-5-yl)-tetrahydro-furan-3R-yl ester

Acetic acid 4R-acetoxy-2R-(2,6-dichloro-purin-9-yl)-5S-(3-ethyl-isoxazol-5-yl)-tetrahydro-furan-3R-yl ester (151mg), (S)-phenylalaninol (53mg) and di-isopropylethylamine (67 l) were dissolved in isopropanol (2ml) and heated at 50°C for 7.5h. The solvent was removed in vacuo to afford the crude title compound as a clear gum. (260mg)

LC/MS (system) R_t = 4.63 min

Mass spectrum m/z 585/587

Example 31

(2R,3R,4S,5S)-2-[6-(1S-hydroxymethyl-2-phenyl-ethylamino)-2-methoxy-purin-9-yl]-5-(3-ethyl-isoxazol-5-yl)-tetrahydrofuran-3,4-diol

Acetic acid 4R-acetoxy-2R-[2-chloro-6-(1S-hydroxymethyl-2-phenyl-ethylamino)-purin-9-yl]-5S-(3-ethyl-isoxazol-5-yl)-tetrahydro-furan-3R-yl ester (259mg) was added to 25% sodium methoxide in methanol (4ml) and the mixture stirred at 22°C for 8h. The solvent was removed in vacuo and the residue purified by flash chromatography over silica gel, eluting with ethyl acetate-methanol (10:1) to give the title compound as a pale yellow gum (101mg).
LC/MS (system A) R_t 4.04 min
Mass spectrum m/z 497 (MH^+)

Experimental details for route (M)

Intermediate 42

(3aS,4S,6R,6aR)-2,2-Dimethyl-6-(6-oxo-1,6-dihydro-purin-9-yl)-cyclopenta[1,3]dioxole-4-carboxylic acid

Potassium permanganate (3.0g) and potassium hydroxide (1.0g) in water (60ml) were stirred together at room temperature overnight and the solution then cooled to O°C. [3aS-(3a ,4 ,6 ,6a)] 1,9-dihydro-9-[tetrahydro-6-(hydroxymethyl)-2,2-dimethyl-4H-cyclopenta-1,3-dioxol-4-yl]-6H-purin-6-one (2.92g) was added slowly such that the temperature of the reaction mixture was maintained below 5°C. The mixture was stirred at room temperature for 5h then cooled to O°C and treated with sodium metabisulfite (4.2g). Hydrochloric acid (5M) was added cautiously to adjust the pH to about 3.5. The solution was stored at 4°C overnight and the resultant precipitate collected, washed with chilled water and dried in vacuo. The title compound was obtained as a white solid (1.82g).

Mass spectrum m/z 321 (MH^+)

Intermediate 43

6-Chloro-9-[2,2-dimethyl-6S-(3-cyclopropyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-(3aS,6aR)-cyclopenta[1,3]dioxol-4R-yl]-9H-purine

(3aS,4S,6R,6aR)-2,2-Dimethyl-6-(6-oxo-1,6-dihydro-purin-9-yl)-cyclopenta [1,3]dioxole-4-carboxylic acid (118mg) in anhydrous chloroform (4.5ml) was heated to reflux with dimethylformamide (29 l) and thionyl chloride (108 l) for 4h. After cooling to room temperature the excess solvent and reagents were removed by evaporation and the residue taken up in anhydrous chloroform (1.5ml). The mixture was added to a cooled (0°C) solution of cyclopropylamidoxime (110mg) and pyridine (41 l) in chloroform (2.5ml). The mixture was heated to reflux for 24h. After cooling, the mixture was evaporated to dryness and the residue purified by flash chromatography on silica gel), eluting with ethyl acetate/cyclohexane (40:60). On evaporation the title compound was obtained as a colourless gum (56mg).

Mass spectrum m/z 403 (MH^+)

Intermediate 44

(1R,2S,3R,5S)-3-(6-Chloro-purin-9-yl)-5-(3-cyclopropyl-[1,2,4]oxadiazol-5-yl)-cyclopentane-1,2-diol

6-Chloro-9-[2,2-dimethyl-6S-(3-cyclopropyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-(3aS,6aR)-cyclopenta[1,3]dioxol-4R-yl]-9H-purine (50mg) was treated with cold (0°C) trifluoroacetic acid-water (2ml; 9:1). The mixture was stored at 4°C overnight and evaporated to dryness. The title compound was obtained as a colourless gum (60mg).

Mass spectrum m/z 363 (MH^+)

Example 32

(1S,2R,3S,5R)-3-(3-cyclopropyl-[1,2,4]oxadiazol-5-yl)-5-[2S-hydroxy-cyclopent-(S)-ylamino-purin-9-yl]-cyclopentane-1,2-diol

(1R,2S,3R,5S)-3-(6-Chloro-purin-9-yl)-5-(3-cyclopropyl-[1,2,4]oxadiazol-5-yl)-cyclopentane-1,2-diol (57mg) in isopropanol (5ml) was treated with trans-

(1S,2S)-2-aminocyclopentanol hydrochloride (34mg) and diisopropylethylamine (85µl) at reflux temperature overnight. The excess solvent was evaporated and the residue purified by automated preparative hplc. The title compound was obtained as a near colourless glass (15mg).

LC/MS (System C): Rt = 2.4 min

Mass spectrum m/z 428 (MH+)

Experimental details for route (N)

Intermediate 45
9-[(3aR,4R,6S,6aR)-6-[3-(tert-butyl)-1,2,4-oxadiazol-5-yl]-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl]-6-(1H-1,2,3-benzotriazol-1-yloxy)-9H-purine

To a solution of (3aS,4S,6R,6aR)-6-(6-chloro-purin-9-yl)-2,2-dimethyl-tetrahydro-furo[3,4-d][1,3]dioxole-4-carboxylic acid (10g) in dimethylformamide (200ml) was added 1-hydroxybenzotriazole (3.96g) and 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (5.62g). t-Butylacetamidoxime (3.40g) in dimethylformamide (30ml) was added and the mixture was stirred at 20°C for 24 h under nitrogen. The mixture was then heated at 70°C for a further 36 h. The resulting mixture was then cooled to 20°C, basified with a saturated solution of sodium bicarbonate (200ml) and extracted with ethyl acetate (2x150ml). The organic layers were washed with brine (300ml), dried ($MgSO_4$), evaporated to dryness *in vacuo* and triturated with ether to give a yellow solid (11.08g). Purification by chromatography on silica gel, eluting with ethyl acetate : cyclohexane (3:7), afforded the title compound (4.75g) as a white solid.

LC/MS (System C): R_t = 3.46 min
Mass Spectrum *m/z* 520 [MH^+]

Intermediate 46:
9-[(3aR,4R,6S,6aR)-6-[3-(tert-butyl)-1,2,4-oxadiazol-5-yl]-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl]-N-isobutyl-9H-purin-6-amine

To a solution of 9-{(3aR,4R,6S,6aR)-6-[3-(tert-butyl)-1,2,4-oxadiazol-5-yl]-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl}-6-(1H-1,2,3-benzotriazol-1-yloxy)-9H-purine (50mg) in dimethylsulfoxide (0.4ml) was added diisopropylethylamine (0.1ml) and isobutylamine (0.038ml). The mixture was stirred at 20°C for 16 h under nitrogen. The mixture was then evaporated to dryness *in vacuo* to give a residue that was purified by automated preparative HPLC to afford the title compound (14mg) as a white compound.

LC/MS (system C): R_t = 3.38

Mass Spectrum *m/z* 458 [MH^+]

Example 45

(2S,3S,4R,5R)-2-[3-(tert-butyl)-1,2,4-oxadiazol-5-yl]-5-[6-(isobutylamino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol

A solution of 9-{(3aR,4R,6S,6aR)-6-[3-(tert-butyl)-1,2,4-oxadiazol-5-yl]-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl}-N-isobutyl-9H-purin-6-amine (14mg) in a cold mixture of trifluoroacetic acid : water (9:1; 1ml) was kept at 4°C for 18 h. The resulting solution was basified in an ice bath with saturated aqueous sodium bicarbonate (20ml), extracted with ethyl acetate (2x20ml), the extracts dried ($MgSO_4$) and evaporated to dryness *in vacuo* to afford the title compound (7.66mg) as a white solid.

LC/MS (System C):R_t = 2.85 min

Mass Spectrum *m/z* 418 [MH^+]

Experimental details for route (O)

Intermediate 47:

9-{(3aR,4R,6S,6aR)-6-[3-(tert-butyl)-1,2,4-oxadiazol-5-yl]-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl}-N-(2,4-difluorophenyl)-9H-purin-6-amine

9-{(3aR,4R,6S,6aR)-6-[3-(tert-butyl)-1,2,4-oxadiazol-5-yl]-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl}-6-(1H-1,2,3-benzotriazol-1-yloxy)-9H-purine (50mg) was dissolved in 2,4-difluoroaniline (0.4ml) and the mixture heated at 80°C for 96 h. The mixture was then cooled to 20°C and partitioned between dichloromethane (25ml) and 1 M hydrochloric acid (15 ml). The separated aqueous phase was further extracted with dichloromethane (1x25 ml) and the combined organic extracts were evaporated to dryness *in vacuo*. Purification by automated preparative HPLC afforded the title compound (18.3 mg) as a dark purple gum.

LC/MS (System C): R_t = 2.85 min
Mass Spectrum *m/z* 418 [MH^+]

Example 49

(2S,3S,4R,5R)-2-[3-(tert-butyl)-1,2,4-oxadiazol-5-yl]-5-[6-(2,4-difluoroanilino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol

A solution of 9-{(3aR,4R,6S,6aR)-6-[3-(tert-butyl)-1,2,4-oxadiazol-5-yl]-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl}-N-(2,4-difluorophenyl)-9H-purin-6-amine (18.3 mg) in a cold mixture of trifluoroacetic acid : water (9:1; 1ml) was kept at 4°C for 18 h. The resulting solution was basified in an ice bath with a saturated solution of sodium bicarbonate (20ml), extracted with ethyl acetate (2x20ml), the extracts dried ($MgSO_4$) and evaporated to dryness *in vacuo* to afford the title compound (14.3mg) as a purple solid.

LC/MS (System C): R_t = 3.03 min
Mass Spectrum *m/z* 474 [MH^+]

Experimental details for route (P)

Intermediate 48:
(3aR,4S,6R,6aR)-6-(6-chloro-9H-purin-9-yl)-N-(2-hydroxypropyl)-2,2 dimethyltetrahydrofuro[3,4-d][1,3]dioxole-4-carboxamide

Thionyl chloride (4.3ml) was added to a stirred solution of (3aS,4S,6R,6aR)-6-(6-chloro-purin-9-yl)-2,2-dimethyl-tetrahydro-furo[3,4-d][1,3]dioxole-4-carboxylic acid (10.0g), in chloroform (100ml). The mixture was heated at reflux temperature under nitrogen for 60 min. After cooling to 20°C the solvent was removed *in vacuo* and the residue azeotroped with toluene (2x50ml). A suspension of the residue in chloroform (50ml) was added dropwise at an equal rate with a solution of 1-amino-2-propanol (2.3ml) and diisopropylethylamine (5.1ml) in chloroform (50ml) over 10 min to chloroform (50ml) at 0°C. The mixture was stirred at 20°C for 18 hours. Phosphate buffer (pH 6.5, 100ml) was added and the phases separated. The aqueous phase was extracted with chloroform (50ml). The combined chloroform layers were dried with sodium sulphate and the solvent removed *in vacuo* to give the title compound as a white foam (6.63g).

Mass spectrum *m/z* 398 [MH^+]

Intermediate 49:
(3aR,4S,6R,6aR)-6-(6-chloro-9H-purin-9-yl)-2,2-dimethyl-N-(2-oxopropyl)tetrahydrofuro[3,4-d][1,3]dioxole-4-carboxamide

To a mixture of (3aR,4S,6R,6aR)-6-(6-chloro-9H-purin-9-yl)-N-(2-hydroxypropyl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxole-4-carboxamide (6.60g) and powdered 4Å molecular sieves (10g) in dichloromethane (165ml) at 0°C, was added acetic acid (3.0ml) followed by the portionwise addition of pyridinium dichromate (9.36g). The mixture was stirred at 0°C for 15 min and then at 20°C for 2 hours. Isopropanol (10ml) was added and the mixture stirred for 15min. Silica gel (Merck 9385, 9.9g) and ethyl acetate (165ml) were added and the reaction stirred for a further 15 min. The mixture was filtered through celite and the filter cake washed with ethyl acetate (300ml). The filtrate was evaporated *in vacuo* to give a brown solid. Purification by flash chromatography on silica gel, eluting with dichloromethane:methanol (100:3) gave a light brown foam. Further purification by chromatography on silica gel (Merck 9385), eluting with ethyl acetate followed by ethyl acetate:methanol (100:2) gave the title compound as a white foam (4.6g).

TLC SiO_2 (ethyl acetate:methanol 100:20) R_f = 0.4

Experimental details for route (Q)

Intermediate 50:
(3aR,4S,6R,6aR)-N-(2-hydroxybutyl)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxole-4-carboxamide

To a solution of furo[3,4-d]-1,3-dioxole-β-D ribofuranose acid (5.0g) in dichloromethane (50ml) was added carbonyl diimidazole (4.83g), the mixture was stirred for 20min at 20°C and 1-amino-2-butanol (2.45g) was added and the mixture was stirred, under nitrogen, at 20°C for 18 h. The mixture was diluted with ether (50ml) and washed with saturated citric acid solution (100ml) and saturated aqueous sodium bicarbonate (100ml). The layers were separated and the organic layers concentrated *in vacuo*; the resulting residue was purified by flash column chromatography on silica gel, eluting with 1:1 ethyl acetate:cyclohexane, to give the title compound as a clear gum (3.81g).

Mass Spectrum *m/z* 290 $[MH]^+$

Intermediate 51:
(3aR,4S,6R,6aR)-6-methoxy-2,2-dimethyl-N-(2-oxobutyl)tetrahydrofuro[3,4-d][1,3]dioxole-4-carboxamide

To a solution of (3aR,4S,6R,6aR)-N-(2-hydroxybutyl)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxole-4-carboxamide (3.81g) in anhydrous dichloromethane (115ml), containing powdered 4Å molecular sieves (5.7g) at 0°C, under nitrogen, were added acetic acid (2.59ml) and potassium dichromate (7.93g), portionwise. The reaction mixture was stirred at 0°C for 15min and at 20°C for a further 2h. The mixture was quenched with isopropanol (40ml) and stirred for 30min, silica gel (Merck 9385) (40g) and ethyl acetate (100ml) were added, and the mixture was stirred for a further 30min. This mixture was filtered through 'harborlite®' filter aid and the filtrate concentrated *in vacuo* to give a crude product which was purified by flash column chromatography on silica gel, eluting with 2:1 ethyl acetate:cyclohexane to give the title compound (1.91g)

^{1}H nmr δ 7.405(1H, br t, -NH), 5.125(1H, br s, CH), 5.095(1H, dd, CH), 4.655(1H, br s, CH), 4.565(1H, d, CH), 4.155(2H, m, CH_2), 3.555(3H, s, OMe), 2.505(2H, q, CH_2), 1.505(3H, s, -Me), 1.355(3H, s, -Me), 1.105(3H, t, $-CH_3$)

Intermediate 52:
2-[(3aR,4S,6R,6aR)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl]-5-ethyl-1,3-oxazole

To a solution of (3aR,4S,6R,6aR)-6-methoxy-2,2-dimethyl-N-(2-oxobutyl)tetrahydrofuro[3,4-d][1,3]dioxole-4-carboxamide (740mg) in dry toluene (10ml), under nitrogen was added phosphorous oxychloride (1.44ml) and the mixture was heated under reflux for 3.5h. The reaction mixture was cooled to 0°C, quenched with saturated aqueous sodium bicarbonate (30mls), stirred vigorously for 30min and extracted with ethyl acetate (4x50ml); the organic layers were combined, washed with brine (30ml), dried ($MgSO_4$) and concentrated *in vacuo* to give a crude product, which was purified by flash column chromatography on silica gel, eluting with a mixture of 5:1 to 7:2 cyclohexane:ethyl acetate, to give the title compound as a yellow oil (0.83g).

Mass Spectrum *m/z* 270 [MH^+]

Intermediate 53:
(2S,3R,4R,5S)-2,4-bis(acetyloxy)-5-(5-ethyl-1,3-oxazol-2-yl)tetrahydrofuran-3-yl acetate

To 2-[(3aR,4S,6R,6aR)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl]-5-ethyl-1,3-oxazole (0.83g) was added 9:1 trifluoroacetic acid:water (3.56ml), and the mixture was stirred at 20°C for 3.5 hours. The solvents were removed *in vacuo* to give an orange/brown oil. This material was dissolved in pyridine (7ml), under nitrogen, acetic anhydride (2.76ml) was added and the mixture was stirred at 22°C for 18h. The mixture was concentrated *in vacuo*, diluted with ethyl acetate (50ml) and washed with 1M HCl (50ml), saturated aqueous sodium bicarbonate (3x50ml) and brine (50ml); the organic layer was dried ($MgSO_4$) and the solvent evaporated to dryness to furnish the title compound as a brown/orange oil (0.854g)

Mass Spectrum m/z *342 [MH$^+$]*

Intermediate 54:

(2R,3R,4R,5S)-4-(acetyloxy)-2-(6-chloro-9H-purin-9-yl)-5-(5-ethyl-1,3-oxazol-2-yl)tetrahydrofuran-3-yl acetate

To 6-chloropurine (0.854g) was added 1,1,1,3,3,3-hexamethyldisilazane (4ml) and toluene (15ml) and the mixture was heated under reflux for 2h. The solvent was removed in vacuo, the residue azeotroped with toluene (1x8ml) and the mixture evaporated to dryness. To this residue was added (2S,3R,4R,5S)-2,4-bis(acetyloxy)-5-(5-ethyl-1,3-oxazol-2-yl)tetrahydrofuran-3-yl acetate (0.854g) in acetonitrile (20ml), trimethylsilyl triflate (0.624ml) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.374ml). The reaction mixture was stirred at 20°C for 18h and at 80°C for 3h and then allowed to cool. The mixture was poured into saturated aqueous bicarbonate (40ml) and extracted with dichloromethane (4x40ml); the organic layers were combined, dried ($MgSO_4$) and the solvent removed *in vacuo* to give a crude product which was purified by flash chromatography on silica gel, eluting with 4:1 then 3:2 cyclohexane:ethyl acetate, to furnish the title compound as a clear gum (355mg).

Mass Spectrum m/z *436 [MH$^+$]*

Example 84

2-({9-[(2R,3R,4S,5S)-5-(5-ethyl-1,3-oxazol-2-yl)-3,4-hydroxytetra hydrofuran-2-yl]-9H-purin-6-yl}amino)-N,N-dimethylethanesulfonamide

To a solution of (2R,3R,4R,5S)-4-(acetyloxy)-2-(6-chloro-9H-purin-9-yl)-5-(5-ethyl-1,3-oxazol-2-yl)tetrahydrofuran-3-yl acetate (50mg) in isopropanol (5ml), N,N-diisopropylethylamine (0.120ml) and N,N-dimethyl-2-aminoethanesulphonamide hydrochloride (86mg) were added. The mixture was stirred at reflux temperature, under nitrogen, for 48h and then cooled. A methanol/ammonia solution (4ml) was added, the mixture was shaken and left

to stand for 24h. The solvent was evaporated and the the resulting residue purified by automated preparative HPLC to give the title product (8.6mg).

Mass Spectrum *m/z* 468 [MH^+]

Experimental details for route (R)

Intermediate 55:
N-{9-[(3aR,4R,6S,6aR)-2,2-dimethyl-6-(3-methyl-1,2,4-oxadiazol-5-yl)tetrahydrofuro[3,4-d][1,3]dioxol-4-yl]-9H-purin-6-yl}-N-cyclopentylamine

A mixture of (3aS,4S,6R,6aR)-6-(6-cyclopentylamino-purin-9-yl)-2,2-dimethyl-tetrahydro-furo[3,4-d][1,3]dioxole-4-carboxylic acid (0.2g), 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (146mg), acetaldoxime (76mg) and dimethoxyethane (DME, 25ml) was heated under reflux for 4 days and then cooled to 22°C. The mixture was concentrated *in vacuo* and ethyl acetate (40ml) added to the residue. The resulting suspension was washed with 0.5M citric acid solution (3x20ml) and the aqueous washings were extracted with ethyl acetate (2x20ml). The combined organic extracts were washed with water (20ml) and brine (30ml) and dried ($MgSO_4$). After concentration *in vacuo* the residue was purified by chromatography on silica gel, eluting with ethyl acetate:cyclohexane (1:1), to give the title compound (63mg).

NMR ($CDCl_3$) δ 8.03 (1H,br.s.,heterocyclic CH); 7.84 (1H,s,heterocyclic CH); 6.29 (1H,br.s,CH); 5.84 (1H,dd,CH); 5.64 (1H,d,CH); 5.48 (1H,d,CH); 4.56 (1H,br.s,CH); 2.19 (3H,s,Me); 1.85-1.5 (9H,m + s, 6x 1/2CH_2 + Me); 1.45 (3H,s,Me); 1.25-0.85 (2H,m,2x 1/2CH_2).

Example 39
(2R,3R,4S,5S)-2-[6-(cyclopentylamino)-9H-purin-9-yl]-5-(3-methyl-1,2,4-oxadiazol-5-yl)tetrahydrofuran-3,4-diol

A mixture of N-{9-[(3aR,4R,6S,6aR)-2,2-dimethyl-6-(3-methyl-1,2,4-oxadiazol-5-yl)tetrahydrofuro[3,4-d][1,3]dioxol-4-yl]-9H-purin-6-yl}-N-cyclopentylamine

(63mg), trifluoroacetic acid (1ml) and water (0.1ml) was stirred at 0° for 6h and then diluted with ethyl acetate (20ml). The mixture was neutralised with sodium bicarbonate solution and the aqueous phase was extracted with ethyl acetate (2x10ml). The combined organic extracts were washed with water (8ml) and brine (10ml) and dried ($MgSO_4$). After concentration *in vacuo* the residue was purified by flahs column chromatography on silica gel, eluting with ethyl acetate:methanol (19:1) to give the title compound as a white foam (42mg).

TLC SiO_2 (ethyl acetate:methanol 19:1) R_f 0.30
NMR (DMSO) δ 8.43 (1H,s,CH); 8.20 (1H,br.s,CH); 7.79 (1H,br.d,NH); 6.45 (2H, v.br.s ,2x OH); 6.16 (1H,d,CH); 5.24 (1H,d,CH); 4.89 (1H,t,CH); 4.73 (1H,t,CH); 4.58 (1H,br.m,CH); 2.42 (3H,s,Me); 2.10-1.50 (8H,m,4xCH_2)

Experimental details for route (S)

Intermediate 56:
1-[(3aR,4R,6R,6aR)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl]pent-1-yn-3-ol

A solution of 4R-ethynyl-6R-methoxy-2,2-dimethyl-tetrahydro-(3aR,6aR)-furo[3,4-d][1,3]dioxole (1.5g) in tetrahydrofuran (20ml) was cooled to -78°C for 15 minutes under nitrogen. A solution of propionaldehyde (1.09ml) in tetrahydrofuran (0.5ml) was added via syringe and stirring continued for 5h. The mixture was allowed to warm to 22°C and stirred for a further 16h. The solvents were removed *in vacuo* and the resultant orange oil partitioned between ether and aqueous ammonium chloride. The organic layers were washed with further aqueous ammonium chloride, dried ($MgSO_4$), and concentrated *in vacuo* to afford a yellow oil. Purification by chromatography on silica gel (Varian Bondelut cartridge), eluting with (i) cyclohexane, (ii) dichloromethane, (iii) ether, (iv) ethyl acetate afforded the title compound as a colourless oil (1.33g).
TLC SiO_2 (ether:cyclohexane 1:1) R_f = 0.39

Intermediate 57:

1-[(3aR,4R,6R,6aR)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl]pent-1-yn-3-one

A solution of 1-[(3aR,4R,6R,6aR)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl]pent-1-yn-3-ol (1.3g) in dichloromethane (100ml) was added to a stirred suspension of manganese dioxide (60g) in dichloromethane at 0°C. The mixture was stirred at 0°C for 3h, filtered through magnesium sulphate (50g) and the solvent removed in vacuo to give the title compound as a colourless oil (550mg).

NMR δ ($CDCl_3$) 5.07 (1H,s,CH); 4.97 (1H,d,CH); 4.93 (1H,s,CH); 4.68 (1H,d,CH); 3.41 (3H,s,OMe); 2.58 (2H,q,CH_2); 1.47 (3H,s,Me); 1.31 (3H,s,Me); 1.14 (3H,t,Me).

Intermediate 58:
1-[(3aR,4R,6R,6aR)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl]pentane-1,3-dione 1-oxime

A mixture of 1-[(3aR,4R,6R,6aR)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl]pent-1-yn-3-one (550mg) and hydroxylamine (50% solution in water) (0.2ml) in ethanol (10ml) was stirred overnight at 22°C. The mixture was concentrated in vacuo to afford the title compound as a yellow oil (554mg). NMR δ ($CDCl_3$) 5.36, 5.31 (1H,2x d,CH); 5.00 (1H,d,CH); 4.92 (1H,d,CH); 4.65 (1H,2x d,CH); 3.40, 3.35 (3H,2x s,OMe); 3.03-2.85 (2H,2x AB,CH_2); 1.92 (2H,m,CH_2); 1.50, 1.34 (6H,2x s,2x Me); 1.03 (3H,2x t,Me).

Intermediate 59:
(3R,4S,5R)-5-(5-ethylisoxazol-3-yl)tetrahydrofuran-2,3,4-triol

1-[(3aR,4R,6R,6aR)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl]pentane-1,3-dione 1-oxime (0.5g) was dissolved in aqueous acetic acid (18mg) and the mixture heated at 100°C for 2h. The solution was cooled and concentrated *in vacuo* to afford a brown oil which was azeotroped with toluene. Purification by chromatography on silica gel (Varian Bondelut silica gel

cartridge), eluting with (i) dichloromethane, (ii) ether, (iii) ethyl acetate, (iv) methanol, gave the title compound (150mg).

TLC SiO_2 (ether) R_f = 0.17

Intermediate 60:
(2R,3R,4R)-4,5-bis(acetyloxy)-2-(5-ethylisoxazol-3-yl)tetrahydrofuran-3-yl acetate

(3R,4S,5R)-5-(5-ethylisoxazol-3-yl)tetrahydrofuran-2,3,4-triol isomer 1 (150mg) was dissolved in pyridine (4ml) and the mixture treated with acetic anhydride (0.983ml). The resulting solution was stirred at 22°C for 18h. The mixture was concentrated *in vacuo* to afford a brown oil. Purification by chromatography on silica gel (Varian Bondelut SiO_2 cartridge), eluting with (i) dichloromethane, (ii) ether (iii) ethyl acetate, afforded the title compound as a pale yellow solid (142mg).

TLC SiO_2 (ether) R_f = 0.53

Intermediate 61:
(2R,3R,4R,5R)-4-(acetyloxy)-2-(2,6-dichloro-9H-purin-9-yl)-5-(5-ethylisoxazol-3-yl)tetrahydrofuran-3-yl acetate

(2R,3R,4R)-4,5-bis(acetyloxy)-2-(5-ethylisoxazol-3-yl)tetrahydrofuran-3-yl acetate isomer 1 (193mg) was dissolved in acetonitrile (5ml) and treated sequentially with 2,6-dichloropurine (213mg), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (0.186ml) and trimethylsilyl trifluoromethanesulphonate (TMSOTf) (0.225ml) via a syringe over 5 min. The clear yellow solution was stirred at 22°C for 40h, at 60°C for 21h, and at 80°C for 6h. The mixture was cooled to room temperature and more DBU (0.186ml) and TMSOTf (0.225ml) were added. After stirring at 22°C for 36h the yellow mixture was heated at 60°C overnight and at 80°C for 6h. The solvents were removed *in vacuo* and the resultant brown oily solid taken up in ethyl acetate and washed with water (20ml, 3:1). The aqueous layer was extracted with ethyl acetate and the combined organic layers dried ($MgSO_4$) and evaporated *in vacuo* to afford a brown oily solid. The

residue was triturated with dichloromethane and a white solid removed by filtration. Evaporation of the filtrate afforded a tan solid. Purification by flash chromatography on silica gel eluting with ether:cyclohexane (1:1) afforded the title compound as a white solid (161mg).

LC/MS (System C) R_t = 3.34min.

Mass spectrum *m/z* 470, 472 [MH^+], [$MH+2^+$]

Intermediate 62:

(2R,3R,4R,5R)-4-(acetyloxy)-2-{2-chloro-6-[(1-ethylpropyl)amino]-9H-purin-9-yl}-5-(5-ethylisoxazol-3-yl)tetrahydrofuran-3-yl acetate

(2R,3R,4R,5R)-4-(acetyloxy)-2-(2,6-dichloro-9H-purin-9-yl)-5-(5-ethylisoxazol-3-yl)tetrahydrofuran-3-yl acetate (125mg) was dissolved in isopropanol (5ml) and the solution was treated with diisopropylethylamine (0.06ml) followed by 1-ethylpropylamine (0.044ml). The mixture was heated at 50°C under nitrogen for 16h. The solvent was removed in vacuo and the mixture partitioned between ethyl acetate and 1M hydrochloric acid. The organic layers were washed with saturated sodium bicarbonate solution and brine, dried ($MgSO_4$) and evaporated in vacuo. Purification by chromatography on silica gel (Varian Bondelut cartridge), eluting with (i) dichloromethane, (ii) ether and (iii) ethyl acetate, gave the title compound as a colourless oil (108mg).

TLC SiO_2 (ether) R_f = 0.26.

Example 163

(2R,3R,4S,5R)-2-{2-chloro-6-[(1-ethylpropyl)amino]-9H-purin-9-yl}-5-(5-ethylisoxazol-3-yl)tetrahydrofuran-3,4-diol formate

A mixture of (2R,3R,4R,5R)-4-(acetyloxy)-2-{2-chloro-6-[(1-ethylpropyl)amino]-9H-purin-9-yl}-5-(5-ethylisoxazol-3-yl)tetrahydrofuran-3-yl acetate (30mg) and 2-morpholinoethylamine (0.037ml) was heated at 90°C for 24h in dimethylsulphoxide (0.5ml). Heating was continued for 60h at 90°C. Purification by preparative HPLC (gradient profile 5-95% (ii) over 18.25min) gave the title compound as a white solid (6mg).

LC/MS (System C) R_t = 3.41 min.

Mass Spectrum *m/z* 437 [MH^+]

Experimental details for route (T)

Intermediate 63:
9-{(3aR,4R,6S,6aR)-6-[5-(tert-butyl)-1,3,4-oxadiazol-2-yl]-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl}-N-(4-chloro-2-fluorophenyl)-9H-purin-6-amine

9-[6S-(5-tert-Butyl-[1,3,4]oxadiazol-2-yl)-2,2-dimethyl-tetrahydro-(3aR,6aS)-furo[3,4-d][1,3]dioxol-4R-yl]-6-chloro-9H-purine (2.8g) was treated with 4-chloro-2-fluoro-aniline (4.48ml), palladium acetate (146mg) and (R)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (620mg) in dry toluene (34ml) and the mixture stirred at room temperature for 5 mins (reaction carried out in seven portions). Caesium carbonate (3.08g, in seven portions) was added, and the mixtures heated at 86-96° C for 16h. The mixtures were combined and partitioned between water (200ml) and dichloromethane (3x120ml). The organic layers were washed with brine, dried ($MgSO_4$) and evaporated *in vacuo* to give a brown oil (8.7g). Purification by chromatography on silica gel, eluting with ethyl acetate:cyclohexane 30:70 gave an off-white solid (2.35g).

LC/MS (System C) R_t = 3.41 min
Mass Spectrum *m/z* 530 [MH^+]

Example 14
(2S,3S,4R,5R)-2-(5-tert-Butyl-[1,3,4]oxadiazol-2-yl)-5-[6-(4-chloro-2-fluoro-phenylamino)-purin-9-yl]-tetrahydro-furan-3,4-diol

9-{(3aR,4R,6S,6aR)-6-[5-(tert-butyl)-1,3,4-oxadiazol-2-yl]-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl}-N-(4-chloro-2-fluorophenyl)-9H-purin-6-amine (2.35g) was dissolved in trifluoroacetic acid (20ml) and water (2ml) with ice bath cooling, and the mixture allowed to stand at 4°C for 17h. The mixture was poured slowly into ice cold saturated aqueous sodium bicarbonate (400ml) and extracted with ethyl acetate (3x200ml). The organic layers were

washed with brine, dried ($MgSO_4$) and evaporated *in vacuo* to give the title compound as a buff solid (2.30g).
LC/MS (System C) R_t = 3.04 min.
Mass Spectrum *m/z* 490 [MH^+]

Experimental details for route (U)

Intermediate 64:
9-[6S-(5-tert-Butyl-[1,3,4]oxadiazol-2-yl)-2,2-dimethyl-tetrahydro-(3aR,6aS)-furo[3,4-d][1,3]dioxol-4R-yl]-6-chloro-9H-purine

1-Deoxy-1-(1,6-dihydro-6-oxo-9H-purin-9-yl)-2,3,-O-(1-methylethylidene)-β-D-ribofuranonic acid[1] (0.4g) was dissolved in tetrahydrofuran (10ml), diisopropylethylamine (0.075ml) was added and the reaction mixture was stirred at 0°C for 10min. Pivaloyl chloride (0.016ml) was then added to the mixture and the reaction was stirred at 0°C for 3h. t-Butylhydrazide trifluoroacetate (0.36g) was dissolved in tetrahydrofuran, cooled to 0°C and treated with diisopropylethylamine (0.24ml); this solution was then added to the reaction mixture. The reaction was allowed to warm up to 20°C and stirred for 20h. The solvent was removed *in vacuo* and the resulting residue purified by flash chromatography (silica gel, eluting with 5% methanol in dichloromethane) to afford the corresponding diacylhydrazide (0.41g).
The diacylhydrazide intermediate (30mg) was dissolved in dimethylformamide (3ml) and cooled to 0°C. Phosphorus oxychloride (45mg) was added, and the reaction mixture stirred at room temperature for 18h, and at 90°C for 2h. The solvent was removed *in vacuo*, and the resulting residue, was purified by automated preparative HPLC to afford the title compound (20mg).

[1] R.A. Olsson et al. J. Med. Chem., 1986, 29, 1683

Experimental details for Route (V)

Intermediate 65:
(2R,3R,4R,5S)-4-(acetyloxy)-5-{3-[(acetyloxy)methyl]isoxazol-5-yl}-2-(6-chloro-9H-purin-9-yl)tetrahydrofuran-3-yl acetate

To 6-chloropurine (1.08g) was added 1,1,1,3,3,3-hexamethyldisilazane (20ml) and the mixture heated at 100°C, under nitrogen for 2.5h. The reaction was allowed to cool, the solvent was removed *in vacuo*, the residue azeotroped with anhydrous toluene (2x2.5ml) and the mixture evaporated to dryness to give an off-white solid. To this solid was added acetic acid 4R-acetoxy-2S-(3-acetoxymethyl-isoxazol-5-yl)-5R-methoxy-tetrahydro-furan-3R-yl ester (450mg) in anhydrous acetonitrile (15ml) under nitrogen, the mixture was cooled to 0°C and trimethylsilyl trifluoromethanesulphonate (1.4ml) added. The mixture was allowed to warm up to 20°C over 20min, then heated to 80°C for 16h. After cooling, the mixture was poured into saturated aqueous sodium bicarbonate (40ml) and extracted with ethyl acetate (3x70ml); the organic layers were combined, washed with brine (50ml), dried ($MgSO_4$) and concentrated to dryness to give a crude porduct which was purified by flash column chromatography on silica gel, eluting with 1:1 ethyl acetate:cyclohexane to furnish the title compound as a clear oil (310mg).

LC/MS (System C) R_t = 2.76min
Mass Spectrum *m/z* 480/482 [MH^+]/ [$MH+2^+$]

Example 155
(2R,3R,4S,5S)-2-(6-{[(1S,2S)-2-hydroxycyclopentyl]amino}-9H-purin-9-yl)-5-[3-(hydroxymethyl)isoxazol-5-yl]tetrahydrofuran-3,4-diol

To a solution of (2R,3R,4R,5S)-4-(acetyloxy)-5-{3-[(acetyloxy)methyl]isoxazol-5-yl}-2-(6-chloro-9H-purin-9-yl)tetrahydrofuran-3-yl acetate (20mg) in isopropyl alcohol (2ml) was added N,N-diisopropylethylamine (0.043ml) and 2-hydroxycyclopentylamine hydrochloride (11.4mg). The mixture was stirred at 50°C, under nitrogen for 18h, cooled and evaporated to dryness *in vacuo*. The resulting residue was purified by automated preparative HPLC (gradient profile 5%-90% (ii) over 20min) to give the intermediate triacetoxy protected product.

To this residue was added methanol (1ml) and t-butylamine (0.013ml) and the mixture was stirred at 0°C for 3 hours. The solvent evaporated *in vacuo* to yield title compound as a white solid (5mg).

LC/MS (System C) R_t = 2.25min
Mass Spectrum *m/z* 419 [MH^+]

Experimental Details for route (W)

Intermediate 66:
(2R,3R,4R,5R)-4-(acetyloxy)-2-ethynyl-5-methoxytetrahydrofuran-3-yl acetate

4R-Ethynyl-6R-methoxy-2,2-dimethyl-tetrahydro-(3aR,6aR)-furo[3,4-d][1,3]dioxole (0.965g) was heated under reflux with conc. hydrochloric acid (1.0ml) in methanol (30ml) for 6h. The methanol was evaporated *in vacuo*, more methanol added, and heating under reflux continued for 16h. Pyridine (1.6ml) was added, the methanol was evaporated *in vacuo*, more methanol was added, and the mixture was evaporated to dryness *in vacuo*. Dry toluene (10ml) was added and the mixture again evaporated to dryness. The residue was dissolved in dry dichloromethane and treated with pyridine (1.6ml), 4-dimethylaminopyridine (25mg), and acetic anhydride (1.37ml), and the mixture was stirred at 22°C under nitrogen for 18h. The mixture was evaporated to dryness *in vacuo* and the residue partitioned between saturated aqueous citric acid (100ml) and dichloromethane (2x75ml). The organic layers were washed with saturated aqueous sodium bicarbonate, dried ($MgSO_4$) and evaporated *in vacuo* to give a pale yellow oil (1.19g).
Purification by chromatography on silica gel (10g Varian Bondelut cartridge), eluting with ethyl acetate: cyclohexane 5:95-30:70) gave the title compound as a colourless oil (724mg).
TLC SiO_2 (Ethyl acetate:cyclohexane 25:75) R_f = 0.3

Intermediate 67:

(2R,3R,4R,5R)-4-(acetyloxy)-2-(6-chloro-9H-purin-9-yl)-5-ethynyltetrahydrofuran-3-yl acetate

6-Chloropurine (250mg) was heated at 130° (oil bath) with hexamethyldisilazane (6ml) with stirring under nitrogen for 2h. The excess reagent was evaporated *in vacuo* and the residue azeotroped with dry toluene (3x5ml) to give a pale yellow solid. (2R,3R,4R,5R)-4-(acetyloxy)-2-ethynyl-5-methoxytetrahydrofuran-3-yl acetate (121mg) was azeotroped with dry toluene (2x5ml), dissolved in dry acetonitrile, and added to the silylated purine, followed by trimethylsilyl trifluoromethanesulphonate (0.334ml). The mixture was heated at 73-74° for 2h. The mixture was poured into saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3x60ml). The organic layers were washed with brine, dried ($MgSO_4$) and evaporated *in vacuo* to give a yellow oil (203mg). Purification by chromatography on silica gel (Varian Bondelut cartridge), eluting with ethyl acetate:cyclohexane 10:90-60:40, gave the title compound as a colourless gum (84mg).
TLC SiO_2 (Ethyl acetate:cyclohexane 50:50) R_f = 0.25

Intermediate 68:
(2R,3R,4R,5R)-4-(acetyloxy)-2-[6-(1H-1,2,3-benzotriazol-1-yloxy)-9H-purin-9-yl]-5-ethynyltetrahydrofuran-3-yl acetate

(2R,3R,4R,5R)-4-(acetyloxy)-2-(6-chloro-9H-purin-9-yl)-5-ethynyltetrahydrofuran-3-yl acetate (104mg) was treated with 1-hydroxybenzotriazole (136mg) in dry DMF (3ml) for 45h at 22°C. The mixture was poured into ice cooled 1M hydrochloric acid (50ml) and extracted with dichloromethane (3x25ml); the organic layers were washed with water (20ml) and saturated aqueous sodium bicarbonate (20ml), dried ($MgSO_4$) and evaporated *in vacuo* to give a colourless gum (148mg).

LC/MS (System C): R_t 3.19 min.
Mass Spectrum *m/z* 464 [MH^+]

Intermediate 69:

(2R,3R,4R,5R)-4-(acetyloxy)-2-[6-(4-chloro-2-fluoroanilino)-9H-purin-9-yl]-5-ethynyltetrahydrofuran-3-yl acetate

(2R,3R,4R,5R)-4-(acetyloxy)-2-[6-(1H-1,2,3-benzotriazol-1-yloxy)-9H-purin-9-yl]-5-ethynyltetrahydrofuran-3-yl acetate was treated with 2-fluoro-4-chloroaniline (0.63ml), and the mixture was heated at 60°C for 22.5h. The mixture was purified by chromatography on silica gel (Varian Bondelut cartridge), eluting with ethyl acetate:cyclohexane 10:90-60:40, to give the title compound (55mg).

TLC SiO_2 (Ethyl acetate:cyclohexane 50:50) R_f = 0.3

Intermediate 70:
(2R,3R,4R,5S)-4-(acetyloxy)-5-(3-bromoisoxazol-5-yl)-2-[6-(4-chloro-2-fluoroanilino)-9H-purin-9-yl]tetrahydrofuran-3-yl acetate

(2R,3R,4R,5R)-4-(acetyloxy)-2-[6-(4-chloro-2-fluoroanilino)-9H-purin-9-yl]-5-ethynyltetrahydrofuran-3-yl acetate (20mg) was stirred at 22°C with dibromoformaldoxime (12.5mg), sodium bicarbonate (39mg), water (0.075ml) and ethyl acetate (1.5ml) for 88h. The mixture was partitioned between water (20ml) and ethyl acetate (3x10ml), the organic layers were washed with brine and evaporated *in vacuo* to give a brown gum (19mg). Purification by chromatography on silica gel (Varian Bondelut cartridge), eluting with ethyl acetate:cyclohexane 20:80-80:20) gave the title compound as a colourless gum (16.8mg).
LC/MS (System C) R_t = 3.6min
Mass Spectrum *m/z* 595, 597 [MH^+], [$MH+2^+$]

Example 164
(2S,3S,4R,5R)-2-(3-bromoisoxazol-5-yl)-5-[6-(4-chloro-2-fluoroanilino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol

(2R,3R,4R,5S)-4-(acetyloxy)-5-(3-bromoisoxazol-5-yl)-2-[6-(4-chloro-2-fluoroanilino)-9H-purin-9-yl]tetrahydrofuran-3-yl acetate (16.8mg) was treated with t-butylamine (0.08ml) in methanol (0.8ml) at 0°C for 1.5h, and the mixture was evaporated to dryness to give the title compound (16mg).

LC/MS (System C) R_t = 3.22min
Mass Spectrum *m/z* 511 [MH^+]

Experimental details for route (Wb)

Example 144
(2R,3R,4S,5S)-2-[6-(4-chloro-2-fluoroanilino)-9H-purin-9-yl]-5-(3-methylisoxazol-5-yl)tetrahydrofuran-3,4-diol

(2R,3R,4R,5R)-4-(acetyloxy)-2-(6-chloro-9H-purin-9-yl)-5-ethynyltetrahydrofuran-3-yl acetate (20mg) was dissolved in anhydrous toluene (0.5ml) and treated with triethylamine (0.006ml), nitroethane (0.004ml) and phenyl isocyanate (0.012ml). The reaction was heated at 100°C for 24h, cooled to room temperature and concentrated *in vacuo*. The resulting residue was purified by automated preparative HPLC, to produce an intermediate which was then dissolved in anhydrous methanol, cooled to 0°C and treated with t-butylamine (0.02ml) for 1h. The reaction mixture was concentrated *in vacuo*, to afford the title compound as a white solid (143mg).

LC/MS (system C) R_t = 2.95min
Mass Spectrum *m/z* 447 [MH^+]

Experimental details for route (X)

Example 130
(2R,3R,4S,5R)-2-[6-(cyclopentylamino)-9H-purin-9-yl]-5-(1,5-dimethyl-1H-1,2,4-triazol-3-yl)tetrahydrofuran-3,4-diol trifluoroacetate

{9-[2,2-Dimethyl-6R-(5-methyl-4H-[1,2,4]triazol-3-yl)-tetrahydro-(3aR,6aR)-furo[3,4-d][1,3]dioxol-4R-yl]-9H-purin-6-yl}-cyclopropyl-amine (250mg) was dissolved in anhydrous toluene (10ml) and treated with dimethylformamide dimethyl acetal (0.47ml). The mixture was heated at reflux temperature for 7h. and then, cooled to 20°C and concentrated *in vacuo*. The resulting residue was purified by flash chromatography on silica gel, eluting with ethyl acetate:

methanol 19:1. The resulting intermediate was treated with a mixture of trifluoroacetic acid /water (9:1) at 0°C for 6h. The reaction mixture was then concentrated *in vacuo*, to afford, after trituration with ethyl acetate, the title compound as a white solid (143mg).

Analysis: Found (%): C 44.4; H 4.8; N 20.4
Required for $C_{18}H_{24}N_8O_3.CF_3CO_2H.1.5\ H_2O$: C 44.4; H 5.2; N 20.7

Experimental details for route (Z)

Intermediate 71:
(2R,3R,4R,5R)-4-(acetyloxy)-2-[(acetyloxy)methyl]-5-[2-chloro-6-(4-chloro-2-fluoroanilino)-9H-purin-9-yl]tetrahydrofuran-3-yl acetate

To a stirred solution of 2,6-dichloro-9-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-9H-purine [2](1.0g) in toluene (25ml) was added palladium acetate (50mg), 4-chloro-2-fluoroaniline (0.5ml) and bis[2-(diphenylphosphino)phenyl] ether [3](120mg) and the reaction stirred at 20°C for 15 min. Caesium carbonate (872mg) was added and the mixture heated at 90°C for 16 hours. The reaction mixture was cooled to 20°C and partitioned between ethyl acetate (100ml) and water (100ml). The organic layer was washed with brine (100ml), dried with magnesium sulphate and the solvent removed *in vacuo*. Purification by flash chromatography on silica gel, eluting with ethyl acetate:cyclohexane (1:1) gave the title compound (400mg).
Mass Spectrum *m/z* 556 [MH^+]

[2] M. J. Robins and B. Uznanski Canad. J. Chem., 1981, 59(17), 2608
[3] J. P. Sadighi, M. C. Harris and S. L. Buchwald Tett. Lett. 1998, 5327-5330

Intermediate 72:
{(3aR,4R,6R,6aR)-6-[2-chloro-6-(4-chloro-2-fluoroanilino)-9H-purin-9-yl]-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl}methanol

To a suspension of (2R,3R,4R,5R)-4-(acetyloxy)-2-[(acetyloxy)methyl]-5-[2-chloro-6-(4-chloro-2-fluoroanilino)-9H-purin-9-yl]tetrahydrofuran-3-yl acetate (400mg) in methanol (7ml), sodium methoxide, 25% in methanol, (3 drops) was added. On stirring for 15 min at 20°C the reaction mixture went clear. On stirring at 20°C for a further 90 min a precipitate formed. The precipitate was collected by filtration and dried *in vacuo* for 16 hours. This was dissolved in a mixture of acetone (15ml) and 2-2-dimethoxypropane (3ml), and para-toluene sulphonic acid (193mg) added. The mixture was stirred at 20°C for 3 hours. The solvent was removed *in vacuo* and the residue dissolved in ethyl acetate (50ml), washed with water (50ml) and brine (30ml), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by chromatography on silica gel (Varian Bondelut cartridge), eluting with cyclohexane:ethyl acetate (1:1) gave the title compound as a white foam (240mg).

Mass Spectrum 470 *m/z* [MH^+]

Experimental details for route (Y)

Intermediate 73:

tert-Butyl 4-[(9-{(2R,3R,4R,5S)-3,4-bis(acetyloxy)-5-[3-(tert-butyl)isoxazol-5-yl]tetrahydrofuran-2-yl}-9H-purin-6-yl)amino]piperidine-1-carboxylate

To a solution of acetic acid 4R-acetoxy-5S-(3-tert-butyl-isoxazol-5-yl)-2R-(6-chloro-purin-9-yl)-tetrahydro-furan-3R-yl ester (455mg) in isopropanol (20ml) was added *tert*-butyl-4-amino-1-piperidinecarboxylate (785mg) and diisopropylethylamine (1.03ml). The mixture was heated at 95°C for 60 h. The resulting mixture was then cooled and evaporated to dryness *in vacuo*. The resulting residue was dissolved in pyridine (20ml) and acetic anhydride (19ml) was added. The mixture was stirred at room temperature for 16h, evaporated to dryness *in vacuo* and redissolved in ethyl acetate (50ml). Citric acid (2 x 50ml) was added to the mixture and the layers separated. The aqueous layers were extracted with ethyl acetate (100ml). The combined ethyl acetate layers were dried ($MgSO_4$), filtered and evaporated to dryness *in vacuo* to afford the title product (500mg) as a yellow solid.

LC/MS (System C): R_t = 3.59 min
Mass Spectrum *m/z* 628 [MH^+]

Intermediate 74:
(2R,3R,4R,5S)-4-(Acetyloxy)-5-[3-(tert-butyl)isoxazol-5-yl]-2-[6-(piperidin-4-ylamino)-9H-purin-9-yl]tetrahydrofuran-3-yl acetate

tert-Butyl 4-[(9-{(2R,3R,4R,5S)-3,4-bis(acetyloxy)-5-[3-(tert-butyl)isoxazol-5-yl]tetrahydrofuran-2-yl}-9H-purin-6-yl)amino]piperidine-1-carboxylate (500mg) was dissolved in trifluoroacetic acid : dichloromethane (1:9, 20ml) and the mixture kept at 3°C for 16h. The mixture was then quenched with saturated sodium bicarbonate solution (100ml) and extracted with dichloromethane (100ml). The organic layer was washed with saturated sodium bicarbonate solution (100ml) and evaporated to dryness *in vacuo* to afford the title compound (407 mg) as a yellow glassy solid.

LC/MS (system C): R_t = 2.45 min
Mass Spectrum *m/z* 528 [MH^+]

Intermediate 75:
(2R,3R,4R,5S)-4-(acetyloxy)-5-[3-(tert-butyl)isoxazol-5-yl]-2-{6-{[1-(methylsulfonyl)piperidin-4-yl]amino}-9H-purin-9-yl}tetrahydrofuran-3-yl acetate

To a solution of (2R,3R,4R,5S)-4-(Acetyloxy)-5-[3-(tert-butyl)isoxazol-5-yl]-2-[6-(piperidin-4-ylamino)-9H-purin-9-yl]tetrahydrofuran-3-yl acetate (40mg) in tetrahydrofuran (4ml) was added methanesulfonyl chloride (0.0088ml) and triethylamine (0.0212ml). The reaction mixture was stirred for 16h at 20°C, and partitioned between ethyl acetate (2x100ml) and water (100ml). The organic layers were washed with water (100ml), dried ($MgSO_4$), and evaporated *in vacuo* to afford the title compound (36.7mg) as a colourless gum.
LC/MS (System C): R_t = 3.20 min
Mass Spectrum *m/z* 606 [MH^+]

Example 167

(2S,3S,4R,5R)-2-[3-(tert-butyl)isoxazol-5-yl]-5-(6-{[1-(methylsulfonyl)piperidin-4-yl]amino}-9H-purin-9-yl)tetrahydrofuran-3,4-diol

(2R,3R,4R,5S)-4-(Acetyloxy)-5-[3-(tert-butyl)isoxazol-5-yl]-2-(6-{[1-(methylsulfonyl)piperidin-4-yl]amino}-9H-purin-9-yl)tetrahydrofuran-3-yl acetate (36.7mg) was dissolved in chilled methanol (2ml) and tert-butylamine (0.038ml) was added at 0°C. The mixture was kept at 3°C for 1.5h, and evaporated *in vacuo* to afford the title compound as a white solid (30.8mg).

LC/MS (System C): R_t = 2.69 min
Mass Spectrum *m/z* 522 [MH^+]

Experimental details for route (Bb)

Intermediate 76:

(2*R*,3*R*,4*R*,5*S*)-4-(acetyloxy)-5-{3-[(acetyloxy)methyl]isoxazol-5-yl}-2-[2-chloro-6-(4-chloro-2-fluoroanilino)-9*H*-purin-9-yl]tetrahydrofuran-3-yl acetate

To acetic acid 4R-acetoxy-5S-(3-acetoxymethyl-isoxazol-5-yl)-2R-(2,6-dichloro-purin-9-yl)-tetrahydro-furan-3R-yl ester (50mg) in toluene (2ml) was added palladium (II) acetate (2.2mg), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (6mg) and 4-chloro-2-fluoroaniline (28.5mg). The mixture was stirred under nitrogen for 20min, cesium carbonate (38mg) was added, and stirring was continued at 80°C for 24h. The mixture was cooled, diluted with ethyl acetate (25ml), washed with water (25ml) and brine (25ml), and evaporated *in vacuo*. Purification by automated preparative HPLC (gradient profile 5-90% (ii) over 18.5min) gave the title compound as a white solid (3.02mg).

LC/MS (System C) R_t = 3.52 min
Mass Spectrum *m/z* = 623 [MH^+]

Intermediate 77:

(2R,3R,4S,5S)-2-[2-chloro-6-(4-chloro-2-fluoroanilino)-9H-purin-9-yl]-5-[3-(hydroxymethyl)isoxazol-5-yl]tetrahydrofuran-3,4-diol

To (2*R*,3*R*,4*R*,5*S*)-4-(acetyloxy)-5-{3-[(acetyloxy)methyl]isoxazol-5-yl}-2-[2-chloro-6-(4-chloro-2-fluoroanilino)-9*H*-purin-9-yl]tetrahydrofuran-3-yl acetate (4.02mg) in methanol (2ml) at 0 °C was added tert-butylamine (0.012ml), and the mixture was allowed to stand at 0 °C for 3h. The solvent was evaporated *in vacuo* to furnish the title compound as a yellow gum (2.48mg).

LC/MS (System C) R_t = 3.10min
Mass Spectrum *m/z* = 497 [MH^+]

Experimental details for Route Cc

Intermediate 78:
(3aR,4S,6R,6aR)-N'-acetyl-6-[6-(4-chloro-2-fluoroanilino)-9H-purin-9-yl]-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxole-4-carbohydrazide

To a stirred solution of (3aR,4S,6R,6aR)-6-[6-(4-chloro-2-fluoroanilino)-9H-purin-9-yl]-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxole-4-carbohydrazide (50mg) in N,N'-dimethylformamide (2ml) at 0°C was added diisopropylethylamine (28µl) and acetyl chloride (9mg). The reaction mixture was stirred at 0 °C for 5h. The mixture was partitioned between ethyl acetate (20ml) and water (20ml). The organic layer was washed with brine (20ml), dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was purified by automated preparative HPLC (gradient profile 5-95% (ii) over 18.5 min) to give the title compound (25mg).

LC/MS : R_t = 2.87 min
Mass Spectrum *m/z* 506 [MH^+]
Subsequent steps analogous to route A.

Reporter Gene Experiments

Agonist activity was measured in Chinese hamster ovary (CHO) cells containing the CRE/SPAP/HYG (CRE = cyclic AMP response element; HYG = hygromycin resistance; SPAP = secreted placental alkaline phosphatase) reporter gene elements, which upon stimulation of cAMP levels produced SPAP. A cell line was used, which was stably transfected with either the human adenosine A1 receptor or the human adenosine A3 receptor in addition to the above elements. Cells were plated out in 96-well plates in culture medium and incubated at 37°C for 1 hour. For measurement of potency, agonists were added to the appropriate wells at a concentration range of approximately 10^{-10} - 10^{-5}M. 15Min later, cAMP levels were stimulated by addition of a maximal concentration of forskolin. All cells were then incubated for a further 5 hours at 37°C, and cooled to room temperature, after which a substrate for the phosphatase (para-nitrophenol phosphate, pNPP), which is converted by SPAP to a coloured reagent) was then added and the 96-well plates were read in a plate reader. From these readings, the concentration-dependence of the inhibition by the agonist for forskolin-stimulated SPAP production can be calculated. One of the agonists tested on each 96-well plate was the standard non-selective agonist, N-ethylcarboxamidoadenosine (NECA), and the potency of all test agonists is expressed relative to that of the NECA standard.

(ECR = equipotent concentration ratio relative to NECA = 1)

Table 2: Potencies in the reporter gene assay

Example No.	Adenosine A1 receptor ECR*	Adenosine A3 receptor ECR*
3	4.16	152
4	5.65	152
6	1.71	134
12	2.28	254
14	5.8	1066.71
16	9.6	201
19	5.15	172

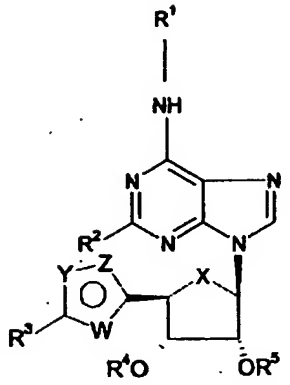
21	23.26	321
22	8.75	423
28	0.42	44.7
37	4.19	507
44	7.68	165.54
45	7.36	165.54
51	7.56	587.75
54	20.78	715.31
56	15.96	717.99
62	29.47	327
67	9.8	827.66
68	4.09	417.37
108	1.52	254
116	27.26	955
119	2.83	154
123	4.19	325.44
126	13.9	
127	0.21	21.62
129	15.5	>199
131	0.15	199.01
132	0.53	>22.4
133	25.47	466.92
134	3.28	>245.4
135	0.48	
136	1.95	
138	1.31	
139	10.64	228
141	12.08	228
143	19.6	>74.1
144	2.8	
145	24.9	
163	1.34	232

164	4.3	
177	2.01	122
178	7.42	>471
179	12.6	
180	18.1	>471
181	8.57	
182	3.48	

*ECR = equipotent concentration ratio relative to NECA = 1 (see description in Reporter Gene Assay)

Claims

1. A compound of formula (I) which is an agonist at the adenosine A1 receptor



(I)

wherein X represents O or CH_2;

R^2 represents C_{1-3}alkyl, C_{1-3}alkoxy, halogen or hydrogen;.

R^3 represents H, phenyl (optionally substituted by halogen), a 5 or 6 membered heteroaryl group, C_{1-6} alkoxy, C_{1-6} alkyl$O(CH_2)_n$ where n is 0-6, C_{3-7} cycloalkyl, C_{1-6} hydroxyalkyl, halogen or a C_{1-6} straight or branched alkyl, C_{1-6} alkenyl or C_{1-6} alkynyl group optionally substituted by one or more halogens.

Y and Z represent O, N, CH, N(C_{1-6} alkyl)
W represents CH, O, N, S, N(C_{1-6} alkyl)
and wherein at least one of W and Z represents a heteroatom (and when Y, Z and/or W is N, the presence or absence of an additional H would be apparent to a person skilled in the art)
with the proviso that when W represents CH, Z represents N and Y represents O, R^3 cannot be H.

R^4 and R^5 independently represent H or a C_{1-6} straight chain or branched alkyl group.

R^1 represents hydrogen or a group selected from

(1) -(alk)$_n$ - (C_{3-7}) cycloalkyl, including bridged cycloalkyl, said cycloalkyl group optionally substituted by one or more substituents selected from OH, halogen, -(C_{1-3}) alkoxy, wherein (alk) represents C_{1-3} alkylene and n represents 0 or 1.

(2) an aliphatic heterocyclic group of 4 to 6 membered rings containing at least one heteroatom selected from O, N or S, optionally substituted by one or more substituents selected from the group consisting of -(C_{1-3})alkyl, -CO_2-(C_{1-4})alkyl, -CO(C_{1-3}alkyl), -S(=O)$_n$-(C_{1-3}alkyl), -CONR^{a}R^b (wherein R^a and R^b independently represent H or C_{1-3}alkyl) or =O; where there is a sulfur atom in the heterocyclic ring, said sulfur is optionally substituted by (=O)$_n$, where n is 1 or 2.

(3) Straight or branched C_{1-12} alkyl, optionally including one or more O, S(=O)$_n$ (where n is 0, 1 or 2) and N groups substituted within the alkyl chain, said alkyl optionally substituted by one or more of the following groups, phenyl, halogen, hydroxy, C_{3-7} cycloalkyl or NR^{a}R^b wherein R^a and R^b independently represent hydrogen, C_{3-7} cycloalkyl or a C_{1-6} straight chain or branched alkyl optionally substituted by C_{3-7} cycloalkyl.

(4) a fused bicyclic aromatic ring

wherein B represents a 5 or 6 membered heterocyclic aromatic group containing 1 or more O, N or S atoms, wherein the bicyclic ring is

attached to the nitrogen atom of formula (I) via a ring atom of ring A and ring B is optionally substituted by $-CO_2-(C_{1-3}alkyl)$.

(5) a phenyl group optionally substituted by one or more substituents selected from:
-halogen, $-SO_3H$, $-(alk)_nOH$, $-(alk)_n$ -cyano, $-(O)_n$ $-(C_{1-6})$alkyl (optionally substituted by one or more halogens), $-(alk)_n$ -nitro, $-(O)_m$ $-(alk)_n-CO_2R^c$,
$-(alk_n)-CONR^cR^d$ $-(alk)_n-COR^c$, $-(alk)_n-SOR^e$, $-(alk)_n-SO_2R^e$, $-(alk)_n-SO_2NR^cR^d$, $-(alk)_nOR^c$, $-(alk)_n-(CO)_m-NHSO_2R^e$, $-(alk)_n-NHCOR^c$, $-(alk)_n-NR^cR^d$ wherein m and n are 0 or 1 and alk represents a C_{1-6}alkylene group or C_{2-6} alkenyl group.

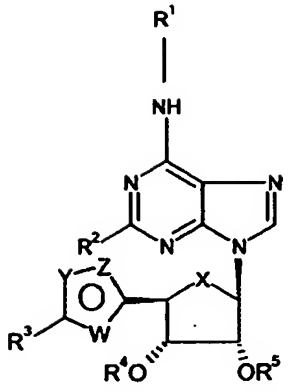
(6) A phenyl group substituted by a 5 or 6 membered heterocyclic aromatic group, said heterocyclic aromatic group optionally being substituted by C_{1-3}alkyl or NR^cR^d.

R^c and R^d may each independently represent hydrogen, or C_{1-3} alkyl or when part of a group NR^cR^d, R^c and R^d together with the nitrogen atom may form a 5 or 6 membered heterocyclic ring optionally containing other heteroatoms, which heterocyclic ring may optionally be substituted further by one or more C_{1-3} alkyl groups.

R^e represents C_{1-3}alkyl

and salts and solvates thereof, in particular, physiologically acceptable solvates and salts thereof for use in therapy.

2. A compound of formula (Ia) which is an agonist at the adenosine A1 receptor



(Ia)

wherein X represents O or CH_2;

R^2 represents C_{1-3}alkyl, C_{1-3}alkoxy, halogen or hydrogen;

R^3 represents H, phenyl (optionally substituted by halogen), a 5 or 6 membered heteroaryl group, C_{1-6} alkoxy, C_{1-6} straight or branched alkyl optionally substituted by one or more halogens, C_{3-7} cycloalkyl, C_{1-6} hydroxyalkyl or halogen.

Y and Z represent O, N, CH
W represents CH, O, N, S
and wherein at least one of W and Z represents a heteroatom (and when Y, Z and/or W is N, the presence or absence of an additional H would be apparent to a person skilled in the art)
with the proviso that when W represents CH, Z represents N and Y represents O, R^3 cannot be H.

R^4 and R^5 independently represent H or a C_{1-6} straight chain or branched alkyl group.

R^1 represents a group selected from

(1) -(alk)$_n$ - (C_{3-7}) cycloalkyl, including bridged cycloalkyl, said cycloalkyl group optionally substituted by one or more substituents selected from OH, halogen, -(C_{1-3}) alkoxy, wherein (alk) represents C_{1-3} alkylene and n represents 0 or 1.

(2) an aliphatic heterocyclic group of 4 to 6 membered rings containing at least one heteroatom selected from O, N or S, optionally substituted by one or more substituents selected from the group consisting of -(C_{1-3})alkyl, -CO_2-(C_{1-4})alkyl, -CO(C_{1-3}alkyl), -S(=O)$_n$-(C_{1-3}alkyl), -CONR^{a}R^b (wherein R^a and R^b independently represent H or C_{1-3}alkyl) or =O; where there is a sulfur atom in the heterocyclic ring, said sulfur is optionally substituted by (=O)$_n$, where n is 1 or 2.

(3) Straight or branched C_{1-12} alkyl, optionally including one or more O, S(=O)$_n$ (where n is 0, 1 or 2) and N groups substituted within the alkyl chain, said alkyl optionally substituted by one or more of the following groups, phenyl, halogen, hydroxy, C_{3-7} cycloalkyl or NR^{a}R^b wherein R^a and R^b independently represent hydrogen, C_{3-7} cycloalkyl or a C_{1-6} straight chain or branched alkyl optionally substituted by C_{3-7} cycloalkyl.

(4) a fused bicyclic aromatic ring

wherein B represents a 5 or 6 membered heterocyclic aromatic group containing 1 or more O, N or S atoms, wherein the bicyclic ring is attached to the nitrogen atom of formula (I) via a ring atom of ring A and ring B is optionally substituted by -CO_2 -(C_{1-3}alkyl).

(5) a phenyl group optionally substituted by one or more substituents selected from:
-halogen, -SO_3H, -(alk)$_n$OH, -(alk)$_n$ -cyano, -(O)$_n$ -(C_{1-6})alkyl (optionally substituted by one or more halogens), - (alk)$_n$ -nitro, -(O)$_m$ -(alk)$_n$- CO_2R^c,

-(alk$_n$)- CONR^{c}R^d -(alk)$_n$ -COR^c, -(alk)$_n$ -SOR^e, -(alk)$_n$ -SO$_2$R^e, -(alk)$_n$-SO$_2$NR^{c}R^d, -(alk)$_n$OR^c, -(alk)$_n$ -(CO)$_m$- NHSO$_2$R^e, -(alk)$_n$- NHCOR^c, -(alk)$_n$- NR^{c}R^d wherein m and n are 0 or 1 and alk represents a C_{1-6}alkylene group or C_{2-6} alkenyl group.

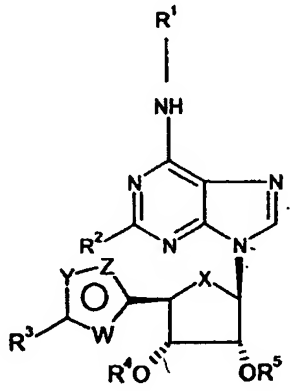
(6) A phenyl group substituted by a 5 or 6 membered heterocyclic aromatic group, said heterocyclic aromatic group optionally being substituted by C_{1-3}alkyl or NR^{c}R^d.

R^c and R^d may each independently represent hydrogen, or C_{1-3} alkyl or when part of a group NR^{c}R^d, R^c and R^d together with the nitrogen atom may form a 5 or 6 membered heterocyclic ring optionally containing other heteroatoms, which heterocyclic ring may optionally be substituted further by one or more C_{1-3} alkyl groups.

R^e represents C_{1-3}alkyl

and salts and solvates thereof, in particular, physiologically acceptable solvates and salts thereof for use in therapy.

3. A compound of formula (Ib) which is an agonist at the adenosine A1 receptor



(Ib)

wherein X represents O or CH_2;

R^2 represents C_{1-3}alkyl, C_{1-3}alkoxy, halogen or hydrogen;

R^3 represents H, phenyl (optionally substituted by halogen), a 5 or 6 membered heteroaryl group, C_{1-6} alkoxy, C_{1-6} alkyl$O(CH_2)_n$ where n is 0-6, C_{3-7} cycloalkyl, C_{1-6} hydroxyalkyl, halogen or a C_{1-6} straight or branched alkyl, C_{1-6} alkenyl or C_{1-6} alkynyl group optionally substituted by one or more halogens.

Y and Z represent O, N, CH, N(C_{1-6} alkyl)
W represents CH, O, N, S, N(C_{1-6} alkyl)
and wherein at least one of W and Z represents a heteroatom (and when Y, Z or W is N, the presence or absence of an additional H would be apparent to a person skilled in the art)
with the proviso that when W represents CH, Z represents N and Y represents O, R^3 cannot be H.

R^4 and R^5 independently represent H or a C_{1-6} straight chain or branched alkyl group.

R^1 represents hydrogen or a group selected from

(1) -$(alk)_n$ - (C_{3-7}) cycloalkyl, including bridged cycloalkyl, said cycloalkyl group optionally substituted by one or more substituents selected from OH, halogen, -(C_{1-3}) alkoxy, wherein (alk) represents C_{1-3} alkylene and n represents 0 or 1.

(2) an aliphatic heterocyclic group of 4 to 6 membered rings containing at least one heteroatom selected from O, N or S, optionally substituted by one or more substituents selected from the group consisting of -(C_{1-3})alkyl, -CO_2-(C_{1-4})alkyl, -CO(C_{1-3}alkyl), -$S(=O)_n$-(C_{1-3}alkyl), -$CONR^aR^b$ (wherein R^a and R^b independently represent H or C_{1-3}alkyl) or =O; where there is a sulfur atom in the heterocyclic ring, said sulfur is optionally substituted by $(=O)_n$, where n is 1 or 2.

(3) Straight or branched C_{1-12} alkyl, optionally including one or more O, $S(=O)_n$ (where n is 0, 1 or 2) and N groups substituted within the alkyl chain, said alkyl optionally substituted by one or more of the following groups, phenyl, halogen, hydroxy, C_{3-7} cycloalkyl or NR^aR^b wherein R^a and R^b independently represent hydrogen, C_{3-7} cycloalkyl or a C_{1-6} straight chain or branched alkyl optionally substituted by C_{3-7} cycloalkyl.

(4) a fused bicyclic aromatic ring

wherein B represents a 5 or 6 membered heterocyclic aromatic group containing 1 or more O, N or S atoms, wherein the bicyclic ring is attached to the nitrogen atom of formula (I) via a ring atom of ring A and ring B is optionally substituted by $-CO_2-(C_{1-3}alkyl)$.

(5) a phenyl group optionally substituted by one or more substituents selected from:
-halogen, $-SO_3H$, $-(alk)_nOH$, $-(alk)_n$ -cyano, $-(O)_n$ $-(C_{1-6})$alkyl (optionally substituted by one or more halogens), $-(alk)_n$ -nitro, $-(O)_m$ $-(alk)_n-CO_2R^c$,
$-(alk_n)-$ $CONR^cR^d$ $-(alk)_n$ $-COR^c$, $-(alk)_n$ $-SOR^e$, $-(alk)_n$ $-SO_2R^e$, $-(alk)_n-SO_2NR^cR^d$, $-(alk)_nOR^c$, $-(alk)_n$ $-(CO)_m-$ $NHSO_2R^e$, $-(alk)_n-$ $NHCOR^c$, $-(alk)_n-$ NR^cR^d wherein m and n are 0 or 1 and alk represents a C_{1-6}alkylene group or C_{2-6} alkenyl group.

(6) A phenyl group substituted by a 5 or 6 membered heterocyclic aromatic group, said heterocyclic aromatic group optionally being substituted by C_{1-3}alkyl or NR^cR^d.

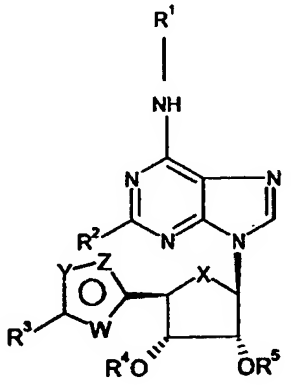
R^c and R^d may each independently represent hydrogen, or C_{1-3} alkyl or when part of a group NR^cR^d, R^c and R^d together with the nitrogen atom may form a 5 or 6 membered heterocyclic ring optionally

containing other heteroatoms, which heterocyclic ring may optionally be substituted further by one or more C_{1-3} alkyl groups.

R^e represents C_{1-3}alkyl with the proviso that when R^4 and R^5 both represent halogen, R^3 cannot represent methyl, ethyl, n-propyl, isopropyl, cyclopropyl, $CH(OH)CH_3$, C_{1-3}alkoxy.

and salts and solvates thereof, in particular, physiologically acceptable solvates and salts thereof.

4. A compound of formula (Ic) which is an agonist at the adenosine A1 receptor



(Ic)

wherein X represents O or CH_2;

R^2 represents C_{1-3}alkyl, C_{1-3}alkoxy, halogen or hydrogen;

R^3 represents H, phenyl (optionally substituted by halogen), a 5 or 6 membered heteroaryl group, C_{1-6} alkoxy, C_{1-6} straight or branched alkyl optionally substituted by one or more halogens, C_{3-7} cycloalkyl, C_{1-6} hydroxyalkyl or halogen.

Y and Z represent O, N, CH

W represents CH, O, N, S
and wherein at least one of W and Z represents a heteroatom (and when Y, Z and/or W is N, the presence or absence of an additional H would be apparent to a person skilled in the art)
with the proviso that when W represents CH, Z represents N and Y represents O, R^3 cannot be H.

R^4 and R^5 independently represent H or a C_{1-6} straight chain or branched alkyl group.

R^1 represents a group selected from

(1) -$(alk)_n$ - (C_{3-7}) cycloalkyl, including bridged cycloalkyl, said cycloalkyl group optionally substituted by one or more substituents selected from OH, halogen, -(C_{1-3}) alkoxy, wherein (alk) represents C_{1-3} alkylene and n represents 0 or 1.

(2) an aliphatic heterocyclic group of 4 to 6 membered rings containing at least one heteroatom selected from O, N or S, optionally substituted by one or more substituents selected from the group consisting of -(C_{1-3})alkyl, -CO_2-(C_{1-4})alkyl, -$CO(C_{1-3}$alkyl), -$S(=O)_n$-$(C_{1-3}$alkyl), -$CONR^aR^b$ (wherein R^a and R^b independently represent H or C_{1-3}alkyl) or =O; where there is a sulfur atom in the heterocyclic ring, said sulfur is optionally substituted by $(=O)_n$, where n is 1 or 2.

(3) Straight or branched C_{1-12} alkyl, optionally including one or more O, $S(=O)_n$ (where n is 0, 1 or 2) and N groups substituted within the alkyl chain, said alkyl optionally substituted by one or more of the following groups, phenyl, halogen, hydroxy, C_{3-7} cycloalkyl or NR^aR^b wherein R^a and R^b independently represent hydrogen, C_{3-7} cycloalkyl or a C_{1-6} straight chain or branched alkyl optionally substituted by C_{3-7} cycloalkyl.

(4) a fused bicyclic aromatic ring

wherein B represents a 5 or 6 membered heterocyclic aromatic group containing 1 or more O, N or S atoms, wherein the bicyclic ring is attached to the nitrogen atom of formula (I) via a ring atom of ring A and ring B is optionally substituted by $-CO_2-(C_{1-3}alkyl)$.

(5) a phenyl group optionally substituted by one or more substituents selected from:
-halogen, $-SO_3H$, $-(alk)_nOH$, $-(alk)_n$ -cyano, $-(O)_n$ $-(C_{1-6})alkyl$ (optionally substituted by one or more halogens), $-(alk)_n$ -nitro, $-(O)_m$ $-(alk)_n-CO_2R^c$,
$-(alk_n)-$ $CONR^cR^d$ $-(alk)_n$ $-COR^c$, $-(alk)_n$ $-SOR^e$, $-(alk)_n$ $-SO_2R^e$, $-(alk)_n-SO_2NR^cR^d$, $-(alk)_nOR^c$, $-(alk)_n$ $-(CO)_m-$ $NHSO_2R^e$, $-(alk)_n-$ $NHCOR^c$, $-(alk)_n-$ NR^cR^d wherein m and n are 0 or 1 and alk represents a C_{1-6}alkylene group or C_{2-6} alkenyl group.

(6) A phenyl group substituted by a 5 or 6 membered heterocyclic aromatic group, said heterocyclic aromatic group optionally being substituted by C_{1-3}alkyl or NR^cR^d.

R^c and R^d may each independently represent hydrogen, or C_{1-3} alkyl or when part of a group NR^cR^d, R^c and R^d together with the nitrogen atom may form a 5 or 6 membered heterocyclic ring optionally containing other heteroatoms, which heterocyclic ring may optionally be substituted further by one or more C_{1-3} alkyl groups.

R^e represents C_{1-3}alkyl with the proviso that when R^4 and R^5 both represent halogen, R^3 cannot represent methyl, ethyl, n-propyl, isopropyl, cyclopropyl, $CH(OH)CH_3$, C_{1-3}alkoxy.

and salts and solvates thereof, in particular, physiologically acceptable solvates and salts thereof.

5. A compound according to claims 1-4 which exhibits little or no agonist activity at the the A3 receptor.

6. A compound according to claims 1-5 wherein the W, Y and Z containing heterocyclic groups include isoxazoles, oxadiazoles, pyrazoles, oxazoles, triazoles, thiadiazoles.

7. A compound according to claims 1-6 wherein the W, Y and Z containing heterocyclic groups are isoxazoles, and 1,2,4- and 1,3,4- oxadiazoles.

8. A compound according to claims 1-7 wherein R^2 represents hydrogen, methyl, methoxy or halogen, more preferably hydrogen or chlorine.

9. A compound according to claims 1-8 wherein R^1 may represent $(alk)_n$- C_{3-6} cycloalkyl wherein n is 0 or 1 and the said cycloalkyl is either substituted by at least one substituent selected from halogen, particularly fluorine, and OH or is unsubstituted and n is zero.

10. A compound according to claim 9 wherein the cycloalkyl group is unsubstituted or monosubstituted with OH.

11. A compound according to claim 10 wherein the cycloalkyl group is 5-membered.

12. A compound according to claims 1-8 wherein R^1 may represent a substituted or unsubstituted aliphatic heterocyclic group, the substitutent being selected from the group consisting of $-CO_2-(C_{1-4})$alkyl

13. A compound according to claim 12 wherein the aliphatic heterocyclic group is unsubstituted or when the substituent is $-CO_2(C_{1-4})$alkyl, the heteroatom is N and the substituent is directly attached to said ring nitrogen atom.

14. A compound according to claims 12-13 wherein the heterocyclic ring is 6 membered.

15. A compound according to claim 14 wherein the heterocyclic ring contains only one O, N or S heteroatom.

16. A compound according to claims 1-8 wherein R^1 may represent a straight or branched alkyl of 1-6 carbon atoms optionally with at least one S $(=O)_n$ and/or N substituted in the chain; where there is an $S(=O)_n$ in the chain, preferably n is 1 or 2 and is unsubstituted or substituted by at least one OH group.

17. A compound according to claims 1-8 wherein R^1 may represent a phenyl group which is substituted by one or two substituents selected from OH, alkyl, particularly C_{1-4} alkyl and halogen.

18. A compound according to claim 17 wherein the phenyl is disubstituted in the 2,4 positions.

19. A compound according to claims 16 and 17 wherein both substituents are halogen.

20. A compound according to any preceding claim wherein R^4 and R^5 both represent hydrogen.

21. A compound selected from:
(2S,3S,4R,5R)-2-(5-tert-Butyl-[1,3,4]oxadiazol-2-yl)-5-[6-(tetrahydro-pyran-4-ylamino)-purin-9-yl]-tetrahydro-furan-3,4-diol;
4-{9-[5S-(5-tert-Butyl-[1,3,4]oxadiazol-2-yl)-3R,4S-dihydroxy-tetrahydro-furan-2R-yl]-9H-purin-6-ylamino}-piperidine-1-carboxylic acid ethyl ester;
(2S,3S,4R,5R)-2-(5-Isopropyl-[1,3,4]oxadiazol-2-yl)-5-[6-(tetrahydro-pyran-4-ylamino)-purin-9-yl]-tetrahydro-furan-3,4-diol;
4-{9-[5S-(5-Cyclopropyl-[1,3,4]oxadiazol-2-yl)-3R,4S-dihydroxy-tetrahydro-furan-2R-yl]-9H-purin-6-ylamino}-piperidine-1-carboxylic acid ethyl ester;
(2S,3S,4R,5R)-2-(5-tert-Butyl-[1,3,4]oxadiazol-2-yl)-5-[6-(4-chloro-2-fluoro-phenylamino)-purin-9-yl]-tetrahydro-furan-3,4-diol;
(2S,3S,4R,5R)-2-(5-Ethyl-oxazol-2-yl)-5-[6-(tetrahydro-pyran-4-ylamino)-purin-9-yl]-tetrahydro-furan-3,4-diol;

(2S,3S,4R,5R)-2-(3-Cyclopropyl-[1,2,4]oxadiazol-5-yl)-5-[6-(2S-hydroxy-cyclopent-(S)-ylamino)-purin-9-yl]-tetrahydro-furan-3,4-diol;
(2S,3S,4R,5R)-2-(3-tert-Butyl-[1,2,4]oxadiazol-5-yl)-5-[6-(2S-hydroxy-cyclopent-(S)-ylamino)-purin-9-yl]-tetrahydro-furan-3,4-diol;
(2S,3S,4R,5R)-2-(3-Cyclopropyl-[1,2,4]oxadiazol-5-yl)-5-[6-(tetrahydro-pyran-4-ylamino)-purin-9-yl]-tetrahydro-furan-3,4-diol;
(2S,3S,4R,5R)-2-(3-tert-Butyl-isoxazol-5-yl)-5-[6-(tetrahydro-pyran-4-ylamino)-purin-9-yl]-tetrahydro-furan-3,4-diol;
ethyl 4-({9-[(2R,3R,4S,5S)-3,4-dihydroxy-5-(3-methyl-1,2,4-oxadiazol-5-yl)tetrahydrofuran-2-yl]-9H-purin-6-yl}amino)piperidine-1-carboxylate;
(2S,3S,4R,5R)-2-[3-(tert-butyl)-1,2,4-oxadiazol-5-yl]-5-{6-[(cyclopropylmethyl)amino]-9H-purin-9-yl}tetrahydrofuran-3,4-diol;
(2S,3S,4R,5R)-2-[3-(tert-butyl)-1,2,4-oxadiazol-5-yl]-5-[6-(isobutylamino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol;
(2R,3R,4S,5S)-2-[6-(cyclopropylamino)-9H-purin-9-yl]-5-(3-isopropyl-1,2,4-oxadiazol-5-yl)tetrahydrofuran-3,4-diol;
2-({9-[(2R,3R,4S,5S)-3,4-dihydroxy-5-(3-isopropyl-1,2,4-oxadiazol-5-yl)tetrahydrofuran-2-yl]-9H-purin-6-yl}amino)-N-methylethanesulfonamide;
(2R,3R,4S,5S)-2-[6-(3,4-difluoroanilino)-9H-purin-9-yl]-5-(3-isopropyl-1,2,4-oxadiazol-5-yl)tetrahydrofuran-3,4-diol;
(2R,3R,4S,5S)-2-[6-(4-chloro-2-fluoroanilino)-9H-purin-9-yl]-5-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)tetrahydrofuran-3,4-diol;
(2R,3S,4R,5R)-2-[5-(tert-butyl)-4H-1,2,4-triazol-3-yl]-5-[6-(4-chloro-2-fluoroanilino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol;
(2R,3R,4S,5R)-2-[6-(2-chloro-4-fluoroanilino)-9H-purin-9-yl]-5-(5-isopropyl-4H-1,2,4-triazol-3-yl)tetrahydrofuran-3,4-diol;
(2S,3S,4R,5R)-2-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)-5-[6-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol;
(2S,3S,4R,5R)-2-[5-(tert-butyl)-1,3,4-oxadiazol-2-yl]-5-[6-(2-chloro-4-fluoroanilino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol;
(2S,3S,4R,5R)-2-[3-(tert-butyl)isoxazol-5-yl]-5-{6-[(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)amino]-9H-purin-9-yl}tetrahydrofuran-3,4-diol;
2-[(9-{(2R,3R,4S,5S)-5-[5-(tert-butyl)-1,3,4-oxadiazol-2-yl]-3,4-dihydroxytetrahydrofuran-2-yl}-9H-purin-6-yl)amino]-N-ethylethanesulfonamide;

2-[(9-{(2R,3R,4S,5S)-5-[5-(tert-butyl)-1,3,4-oxadiazol-2-yl]-3,4-dihydroxytetrahydrofuran-2-yl}-9H-purin-6-yl)amino]-N-(3-methylphenyl)ethanesulfonamide;
2-({9-[(2R,3R,4S,5S)-3,4-dihydroxy-5-(5-methyl-1,3-oxazol-2-yl)tetrahydrofuran-2-yl]-9H-purin-6-yl}amino)-N-methylethanesulfonamide;
(2R,3R,4S,5S)-2-[6-(cyclopentylamino)-9H-purin-9-yl]-5-[3-(methoxymethyl)-1,2,4-oxadiazol-5-yl]tetrahydrofuran-3,4-diol;
(2S,3S,4R,5R)-2-(5-ethyl-1,3,4-oxadiazol-2-yl)-5-[6-(isopropylamino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol;
(2R,3R,4S,5S)-2-(6-{[(1S,2S)-2-hydroxycyclopentyl]amino}-9H-purin-9-yl)-5-(5-methyl-1,3,4-oxadiazol-2-yl)tetrahydrofuran-3,4-diol;
(2R,3R,4S,5S)-2-{2-chloro-6-[(1-ethylpropyl)amino]-9H-purin-9-yl}-5-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)tetrahydrofuran-3,4-diol formate (1:2);
(2R,3R,4S,5S)-2-[2-Chloro-6-(1-ethyl-propylamino)-purin-9-yl]-5-(3-cyclopropyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol diformate;
(2S,3S,4R,5R)-2-(3-ethylisoxazol-5-yl)-5-[6-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol;
(2S,3S,4R,5R)-2-(3-ethylisoxazol-5-yl)-5-(6-{[(1S,2S)-2-hydroxycyclopentyl]amino}-9H-purin-9-yl)tetrahydrofuran-3,4-diol;
ethyl 4-({9-[(2R,3R,4S,5S)-5-(3-ethylisoxazol-5-yl)-3,4-dihydroxytetrahydrofuran-2-yl]-9H-purin-6-yl}amino)piperidine-1-carboxylate;
(2R,3S,4R,5R)-2-[5-(tert-butyl)-4H-1,2,4-triazol-3-yl]-5-[6-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol;
(2R,3S,4R,5R)-2-(5-isopropyl-4H-1,2,4-triazol-3-yl)-5-[6-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol;
(2R,3R,4S,5S)-2-[2-chloro-6-(2-chloro-4-fluoroanilino)-9H-purin-9-yl]-5-(5-methyl-1,3-oxazol-2-yl)tetrahydrofuran-3,4-diol;
(2R,3R,4S,5S)-2-[6-(4-chloro-2-fluoroanilino)-9H-purin-9-yl]-5-(3-methylisoxazol-5-yl)tetrahydrofuran-3,4-diol;
(2R,3R,4S,5S)-2-[6-(4-chloro-2-fluoroanilino)-9H-purin-9-yl]-5-(3-propylisoxazol-5-yl)tetrahydrofuran-3,4-diol;
(2R,3R,4S,5S)-2-[2-chloro-6-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl]-5-(3-ethylisoxazol-5-yl)tetrahydrofuran-3,4-diol;
ethyl 4-({2-chloro-9-[(2R,3R,4S,5S)-5-(3-ethylisoxazol-5-yl)-3,4-dihydroxytetrahydrofuran-2-yl]-9H-purin-6-yl}amino)piperidine-1-carboxylate;

(2R,3R,4S,5S)-2-(2-chloro-6-{[(1S,2S)-2-hydroxycyclopentyl]amino}-9H-purin-9-yl)-5-(3-ethylisoxazol-5-yl)tetrahydrofuran-3,4-diol;
(2R,3R,4S,5S)-2-(2-chloro-6-{[2-(ethylsulfonyl)ethyl]amino}-9H-purin-9-yl)-5-(3-ethylisoxazol-5-yl)tetrahydrofuran-3,4-diol;
(2R,3R,4S,5S)-2-[2-chloro-6-(4-chloro-2-fluoroanilino)-9H-purin-9-yl]-5-(3-ethylisoxazol-5-yl)tetrahydrofuran-3,4-diol;
(2R,3R,4S,5S)-2-[2-chloro-6-(2-chloro-4-fluoroanilino)-9H-purin-9-yl]-5-(3-ethylisoxazol-5-yl)tetrahydrofuran-3,4-diol;
(2R,3R,4S,5S)-2-[2-chloro-6-(2-fluoroanilino)-9H-purin-9-yl]-5-(3-ethylisoxazol-5-yl)tetrahydrofuran-3,4-diol;
(2R,3R,4S,5S)-2-[2-chloro-6-(2-chloroanilino)-9H-purin-9-yl]-5-(3-ethylisoxazol-5-yl)tetrahydrofuran-3,4-diol;
(2R,3R,4S,5S)-2-(6-{[(1S,2S)-2-hydroxycyclopentyl]amino}-9H-purin-9-yl)-5-[3-(hydroxymethyl)isoxazol-5-yl]tetrahydrofuran-3,4-diol;
ethyl 4-[(9-{(2R,3R,4S,5S)-3,4-dihydroxy-5-[3-(hydroxymethyl)isoxazol-5-yl]tetrahydrofuran-2-yl}-9H-purin-6-yl)amino]piperidine-1-carboxylate;
(2S,3S,4R,5R)-2-[3-(hydroxymethyl)isoxazol-5-yl]-5-[6-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol;
(2R,3R,4S,5S)-2-[6-(4-chloro-2-fluoroanilino)-9H-purin-9-yl]-5-(3-ethylisoxazol-5-yl)tetrahydrofuran-3,4-diol;
(2R,3R,4S,5S)-2-[6-(2-chloro-4-fluoroanilino)-9H-purin-9-yl]-5-(3-ethylisoxazol-5-yl)tetrahydrofuran-3,4-diol;
(2S,3S,4R,5R)-2-(3-ethylisoxazol-5-yl)-5-[6-(2-fluoroanilino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol;
(2R,3R,4S,5S)-2-[6-(2-chloroanilino)-9H-purin-9-yl]-5-(3-ethylisoxazol-5-yl)tetrahydrofuran-3,4-diol;
(2S,3S,4R,5R)-2-[5-(tert-butyl)-1,3,4-oxadiazol-2-yl]-5-[6-(piperidin-4-ylamino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol;
(2R,3R,4S,5R)-2-{2-chloro-6-[(1-ethylpropyl)amino]-9H-purin-9-yl}-5-(5-ethylisoxazol-3-yl)tetrahydrofuran-3,4-diol formate;
(2S,3S,4R,5R)-2-(3-bromoisoxazol-5-yl)-5-[6-(4-chloro-2-fluoroanilino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol;
(2S,3S,4R,5R)-2-[3-(tert-butyl)isoxazol-5-yl]-5-(6-{[1-(methylsulfonyl)piperidin-4-yl]amino}-9H-purin-9-yl)tetrahydrofuran-3,4-diol;

(2S,3S,4R,5R)-2-[3-(tert-butyl)isoxazol-5-yl]-5-(6-{[1-(propylsulfonyl)piperidin-4-yl]amino}-9H-purin-9-yl)tetrahydrofuran-3,4-diol;
(2S,3S,4R,5R)-2-[3-(tert-butyl)isoxazol-5-yl]-5-(6-{[1-(isopropylsulfonyl)piperidin-4-yl]amino}-9H-purin-9-yl)tetrahydrofuran-3,4-diol;
(2S,3S,4R,5R)-2-[3-(tert-butyl)isoxazol-5-yl]-5-(6-{[1-(ethylsulfonyl)piperidin-4-yl]amino}-9H-purin-9-yl)tetrahydrofuran-3,4-diol;
(2S,3S,4R,5R)-2-[3-(tert-butyl)isoxazol-5-yl]-5-[2-chloro-6-(4-chloro-2-fluoroanilino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol;
(2S,3S,4R,5R)-2-[3-(tert-butyl)isoxazol-5-yl]-5-[2-chloro-6-(2-chloro-4-fluoroanilino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol;
2-[(9-{(2R,3R,4S,5S)-5-[3-(tert-butyl)isoxazol-5-yl]-3,4-dihydroxytetrahydrofuran-2-yl}-2-chloro-9H-purin-6-yl)amino]-N-ethylethanesulfonamide;
2-[(9-{(2R,3R,4S,5S)-5-[3-(tert-butyl)isoxazol-5-yl]-3,4-dihydroxytetrahydrofuran-2-yl}-2-chloro-9H-purin-6-yl)amino]-N-isopropylethanesulfonamide;
(2S,3S,4R,5R)-2-[3-(tert-butyl)isoxazol-5-yl]-5-[2-chloro-6-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol;
(2R,3R,4S,5S)-2-[6-(4-chloro-2-fluoroanilino)-9H-purin-9-yl]-5-(3-pyridin-3-ylisoxazol-5-yl)tetrahydrofuran-3,4-diol;
(2R,3R,4S,5S)-2-[6-(4-chloro-2-fluoroanilino)-9H-purin-9-yl]-5-[3-(4-hydroxybutyl)isoxazol-5-yl]tetrahydrofuran-3,4-diol;
2-[(9-{(2R,3R,4S,5S)-5-[3-(tert-butyl)isoxazol-5-yl]-3,4-dihydroxytetrahydrofuran-2-yl}-9H-purin-6-yl)amino]-N-ethylethanesulfonamide;
(2R,3R,4S,5S)-2-[6-(cyclopentylamino)-9H-purin-9-yl]-5-[5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl]tetrahydrofuran-3,4-diol;
(2R,3R,4S,5S)-2-(6-{[(1S,2S)-2-hydroxycyclopentyl]amino}-9H-purin-9-yl)-5-[5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl]tetrahydrofuran-3,4-diol;
ethyl 4-[(9-{(2R,3R,4S,5S)-3,4-dihydroxy-5-[5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl]tetrahydrofuran-2-yl}-9H-purin-6-yl)amino]piperidine-1-carboxylate;
(2R,3R,4S,5S)-2-[6-(4-chloro-2-fluoroanilino)-9H-purin-9-yl]-5-(5-methyl-1,3,4-oxadiazol-2-yl)tetrahydrofuran-3,4-diol;
(2R,3R,4S,5S)-2-[6-(4-chloro-2-fluoroanilino)-9H-purin-9-yl]-5-(3-cyclopropylisoxazol-5-yl)tetrahydrofuran-3,4-diol;
(2S,3S,4R,5R)-2-[3-(tert-butyl)isoxazol-5-yl]-5-{6-[(1-butyrylpiperidin-4-yl)amino]-9H-purin-9-yl}tetrahydrofuran-3,4-diol;

isopropyl 4-[(9-{(2R,3R,4S,5S)-5-[3-(tert-butyl)isoxazol-5-yl]-3,4-dihydroxytetrahydrofuran-2-yl}-9H-purin-6-yl)amino]piperidine-1-carboxylate;
(2S,3S,4R,5R)-2-[3-(tert-butyl)isoxazol-5-yl]-5-(6-{[1-(2,2,2-trifluoroacetyl)piperidin-4-yl]amino}-9H-purin-9-yl)tetrahydrofuran-3,4-diol;
methyl 4-[(9-{(2R,3R,4S,5S)-5-[3-(tert-butyl)isoxazol-5-yl]-3,4-dihydroxytetrahydrofuran-2-yl}-9H-purin-6-yl)amino]piperidine-1-carboxylate;
(2R,3R,4S,5S)-2-[6-(4-chloro-2-fluoroanilino)-9H-purin-9-yl]-5-[3-(hydroxymethyl)isoxazol-5-yl]tetrahydrofuran-3,4-diol;
(2R,3R,4S,5S)-2-[6-(2-chloro-4-fluoroanilino)-9H-purin-9-yl]-5-[3-(hydroxymethyl)isoxazol-5-yl]tetrahydrofuran-3,4-diol;
(2R,3R,4S,5S)-2-[6-(2-fluoroanilino)-9H-purin-9-yl]-5-[3-(hydroxymethyl)isoxazol-5-yl]tetrahydrofuran-3,4-diol;
(2R,3R,4S,5S)-2-[6-(2-chloroanilino)-9H-purin-9-yl]-5-[3-(hydroxymethyl)isoxazol-5-yl]tetrahydrofuran-3,4-diol;
(2R,3R,4S,5S)-2-(2-chloro-6-{[(1S,2S)-2-hydroxycyclopentyl]amino}-9H-purin-9-yl)-5-[3-(hydroxymethyl)isoxazol-5-yl]tetrahydrofuran-3,4-diol;
(2R,3R,4S,5S)-2-[2-chloro-6-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl]-5-[3-(hydroxymethyl)isoxazol-5-yl]tetrahydrofuran-3,4-diol;
2-[(2-chloro-9-{(2R,3R,4S,5S)-3,4-dihydroxy-5-[3-(hydroxymethyl)isoxazol-5-yl]tetrahydrofuran-2-yl}-9H-purin-6-yl)amino]-N-ethylethanesulfonamide;
ethyl 4-[(2-chloro-9-{(2R,3R,4S,5S)-3,4-dihydroxy-5-[3-(hydroxymethyl)isoxazol-5-yl]tetrahydrofuran-2-yl}-9H-purin-6-yl)amino]piperidine-1-carboxylate;
(2R,3R,4S,5S)-2-[2-chloro-6-(4-chloro-2-fluoroanilino)-9H-purin-9-yl]-5-[3-(hydroxymethyl)isoxazol-5-yl]tetrahydrofuran-3,4-diol;
(2R,3R,4S,5S)-2-[2-chloro-6-(2-chloro-4-fluoroanilino)-9H-purin-9-yl]-5-[3-(hydroxymethyl)isoxazol-5-yl]tetrahydrofuran-3,4-diol;
(2R,3R,4S,5S)-2-[2-chloro-6-(2-fluoroanilino)-9H-purin-9-yl]-5-[3-(hydroxymethyl)isoxazol-5-yl]tetrahydrofuran-3,4-diol;
(2S,3S,4R,5R)-2-(3-ethylisoxazol-5-yl)-5-[2-methoxy-6-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol;
ethyl 4-({9-[(2R,3R,4S,5S)-5-(3-ethylisoxazol-5-yl)-3,4-dihydroxytetrahydrofuran-2-yl]-2-methoxy-9H-purin-6-yl}amino)piperidine-1-carboxylate;
(2S,3S,4R,5R)-2-(3-ethylisoxazol-5-yl)-5-(6-{[(1S,2S)-2-hydroxycyclopentyl]amino}-2-methoxy-9H-purin-9-yl)tetrahydrofuran-3,4-diol;

(2S,3S,4R,5R)-2-(3-ethylisoxazol-5-yl)-5-(6-{[2-(ethylsulfonyl)ethyl]amino}-2-methoxy-9H-purin-9-yl)tetrahydrofuran-3,4-diol;
(2R,3R,4S,5S)-2-[6-(2-chloro-4-fluoroanilino)-2-methoxy-9H-purin-9-yl]-5-(3-ethylisoxazol-5-yl)tetrahydrofuran-3,4-diol;
(2S,3S,4R,5R)-2-(3-ethylisoxazol-5-yl)-5-[6-(2-fluoroanilino)-2-methoxy-9H-purin-9-yl]tetrahydrofuran-3,4-diol;
(2R,3R,4S,5S)-2-[6-(4-chloro-2-fluoroanilino)-2-methoxy-9H-purin-9-yl]-5-(3-ethylisoxazol-5-yl)tetrahydrofuran-3,4-diol;
(2S,3S,4R,5R)-2-[3-(tert-butyl)-1,2,4-oxadiazol-5-yl]-5-[6-(cyclopropylamino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol;
(2S,3S,4R,5R)-2-[5-(tert-butyl)-1,3,4-oxadiazol-2-yl]-5-[2-chloro-6-(4-chloro-2-fluoroanilino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol;
(2R,3R,4S,5S)-2-[6-(4-chloro-2-fluoroanilino)-9H-purin-9-yl]-5-(5-isopropyl-1,3,4-oxadiazol-2-yl)tetrahydrofuran-3,4-diol.

22. A pharmaceutical composition comprising compounds of claims 1-21 together with a pharmaceutically acceptable diluent or carrier.

23. Use of a compound according to claims 1-21 for the manufacture of a medicament for the treatment of a patient suffering from a condition where there is an advantage in decreasing plasma free fatty acid concentration, or reducing heart rate or which subject is suffering from or susceptible to ischaemic heart disease, peripheral vascular disease or stroke or which subject is suffering pain, a CNS disorder or sleep apnoea.

24. A method of treating a patient suffering from a condition where there is an advantage in decreasing plasma free fatty acid concentration, or reducing heart rate or which subject is suffering from or susceptible to ischaemic heart disease, peripheral vascular disease or stroke or which subject is suffering pain, a CNS disorder or sleep apnoea comprising administration of a therapeutically effective amount of a compound of claims 1-21.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 99/04182

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07H19/16 A61K31/70

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07H C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 01459 A (NOVONORDISK AS) 15 January 1998 (1998-01-15) cited in the application claims	1-24
A	WO 98 01426 A (CHOI SLEDESKI YONG MI ;PAULS HENRY W (US); EWING WILLIAM R (US); M) 15 January 1998 (1998-01-15) cited in the application claims	1-24
A	WO 98 16539 A (NOVONORDISK AS ;KNUTSEN LARS (GB)) 23 April 1998 (1998-04-23) cited in the application claims	1-24

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 October 1999	13/10/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Chouly, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int tional Application No
PCT/EP 99/04182

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
P,A	WO 98 28319 A (GEDEN JOANNA VICTORIA ;COX BRIAN (GB); HOBBS HEATHER (GB); GLAXO G) 2 July 1998 (1998-07-02) claims	1-24

1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 99/04182

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 24
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim 24 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int tional Application No
PCT/EP 99/04182

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9801459 A	15-01-1998	AU 3255097 A	02-02-1998
WO 9801426 A	15-01-1998	AU 3645497 A	02-02-1998
		CZ 9900024 A	12-05-1999
		EP 0912520 A	06-05-1999
		NO 990063 A	08-03-1999
		PL 331036 A	21-06-1999
WO 9816539 A	23-04-1998	AU 4377397 A	11-05-1998
WO 9828319 A	02-07-1998	AU 5762298 A	17-07-1998
		NO 993114 A	23-08-1999